

1 IN THE UNITED STATES DISTRICT COURT

2 IN AND FOR THE DISTRICT OF DELAWARE

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4 RESEARCH FOUNDATION OF STATE
UNIVERSITY OF NEW YORK, et al., : CIVIL ACTION

5 Plaintiffs, :

:

6 v. :

:

7 MYLAN PHARMACEUTICALS, INC., :
: NO. 09-184-LPS

8 Defendant. :

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MYLAN PHARMACEUTICALS, INC., :

: CIVIL ACTION

10 Plaintiff, :

:

11 v. :

:

12 GALDERMA LABORATORIES, INC., :

13 GALDERMA LABORATORIES, L.P., and :

SUPERNUS PHARMACEUTICALS, INC., : NO. 10-892-LPS

:

14 Defendants.

15 - - -

16 Wilmington, Delaware

Tuesday, July 5, 2011

BENCH TRIAL - VOLUME A

18 - - -
19 BEFORE: HONORABLE **LEONARD P. STARK**, U.S.D.C.J.

20 APPEARANCES: - - -

21 MORRIS NICHOLS ARSHT & TUNNELL, LLP

22 BY: JACK B. BLUMENFELD, ESQ.

23 and

24 Brian P. Gaffigan
Kevin Maurer
25 Official Court Reporters

1 APPEARANCES (Continued) :

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3 PAUL HASTING JANOFSKY & WALKER, LLP
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5 CHRISTINE WILLGOOS, ESQ.,
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7 MELANIE R. RUPERT, ESQ.
8 (New York, New York)

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10 Counsel for Research Foundation of
11 State University of New York, Galderma
12 Laboratories, Inc., New York University,
13 Galderma Laboratories, L.P., and
14 Supernus Pharmaceuticals, Inc.

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19 and

20 WILSON SONSINI GOODRICH & ROSATI, PC
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36 Counsel on behalf of
37 Mylan Pharmaceuticals, Inc.

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PROCEDINGS

(REPORTER'S NOTE: The following trial
proceedings was held in open court, beginning at 8:35 a.m.)

THE COURT: Good morning, everyone.

10 MR. BLUMENFELD: Good morning, your Honor.

11 THE COURT: Good morning.

12 MR. BLUMENFELD: Jack Blumenfeld for the
13 Galderma parties, along with Gerald Flattmann, Christine
14 Willgoos, Joe O'Malley, Melanie Rupert, all of Paul
15 Hastings.

16 We have a lot of other people in the back. One
17 is in-house counsel at Galderma, Quinton Cassidy.

18 THE COURT: Welcome to all of you.

19 (The attorneys respond, "good morning, your
20 Honor.")

21 MR. HORWITZ: Good morning, your Honor.

22 THE COURT: Good morning.

23 MR. HORWITZ: Rich Horwitz from Potter Anderson
24 on behalf of Mylan.

I think you know everyone at counsel table but,

1 David Steuer, Tung-On Kong, Matthew Reed, all from Wilson
2 Sonsini.

3 Also in front of the bar, Lori Westin from
4 Wilson Sonsini, and Joseph Divinagracia from Mylan.

5 THE COURT: Thank you. Good morning to all of
6 you as well.

7 So we are here for trial. Before I bring up one
8 issue, I did want to see if there are any issues either of
9 the parties wish to raise before we get started this
10 morning. Is there anything from the plaintiffs?

11 MR. FLATTMANN: No, your Honor.

12 THE COURT: And anything from the defendant?

13 MR. STEUER: No, your Honor. We do have a few
14 document issues but I don't think we need to take them up
15 yet.

16 THE COURT: Okay. They're not for today?

17 MR. STEUER: They are for today.

18 THE COURT: If they are for today, then we
19 should take them up now.

20 MR. STEUER: Okay. Mr. Reed will take care of
21 that.

22 THE COURT: Okay. Give me your name again.

23 MR. REED: Matthew Reed.

24 THE COURT: Reed.

25 MR. REED: Yes. There are two categories of

1 documents that the plaintiffs have identified as exhibits
2 they intend to use today. On the first, we really just seek
3 clarification from the Court. The first category consists
4 of the Court's claim construction orders and stipulation
5 between the parties regarding claim construction. We had
6 indicated that we didn't believe that those documents should
7 be admitted into evidence. I'm not sure of the plaintiffs'
8 position on that. We have no problem with the use of those
9 documents obviously at the trial but do not believe that
10 they should be admitted into evidence.

11 THE COURT: Go on to the second one.

12 MR. REED: The second category of documents
13 include documents that have been identified as ones they
14 intend to use with several of their expert witnesses today.
15 Those documents consist of documents that again we have no
16 issue with their admission into evidence, but we do take
17 issue with their experts testifying regarding those
18 documents because they had never previously been identified
19 as documents that the experts had considered relied upon or
20 intended to offer opinions on.

21 THE COURT: So is that an objection that any
22 testimony by those experts about those documents would be
23 beyond the scope of the experts disclosed?

24 MR. REED: Exactly.

25 THE COURT: Let me see what Mr. Flattmann or

1 whomever from the plaintiffs have to say about these two
2 categories.

3 MR. FLATTMANN: Ms. Willgoos will address the
4 objections.

5 THE COURT: I didn't mean to cut you off,
6 Ms. Willgoos. I just saw Mr. Flattmann rising. Go ahead.

7 MS. FLATTMANN: No problem, your Honor. As for
8 the first category of documents, those are on the record
9 already. We have no intent to put those into evidence.

10 As for the second category of documents, I
11 believe there are only two at issue that we intend to use
12 that had been objected to. One of those may have been
13 resolved. I'm not entirely clear on Mylan's position on
14 that. But DTX-2267 is in Dr. Rudnic's report, was cited at
15 paragraph 52 and PTX-221 was also cited in Dr. Rudnic's
16 report and we do intend to put that into evidence as well.
17 That is PTX, yes, 221. Thank you.

18 THE COURT: Thank you. On the first one, it
19 seems there is no dispute. No one is going to offer them
20 into evidence so there is nothing to decide there.

21 On the expert documents, I'll just reiterate the
22 standard approach of this court to all objections of expert
23 testimony beyond the scope of what has been disclosed
24 previously by the expert, which is if you believe, if they
25 go ahead and offer that evidence, it will be admitted today.

1 And if you believe following trial that they have gone
2 beyond the scope of what previously had been disclosed, you
3 can renew that objection post-trial, and if you prevail on
4 that objection and a new trial is necessitated, they will
5 bear all the costs for the new trial.

6 Anything else from defendants?

7 MR. REED: I think that resolves it.

8 THE COURT: Okay. Fine. The only issue that I
9 had was you all provided me with objections for just one
10 deposition witness who, in this case, the plaintiffs intend
11 to offer today. And this is the deposition testimony of
12 Mr. Talton and Mylan has several objections which is listed
13 in the letter of July 3rd. We've reviewed the objections
14 and the proposed testimony and all of those objections are
15 overruled. In the Court's view the testimony of Mylan's
16 Vice President of Regulatory Affairs, Mr. Talton who signed
17 Mylan's proposed ANDA's testimony about the label and his
18 knowledge and Mylan's knowledge of its contents and veracity
19 of the label, in the Court's view, that is relevant and not
20 hearsay.

21 The Court will give it the weight it deserves
22 after hearing the testimony from Mr. Talton and all other
23 evidence that is in the record, including from the person
24 who Mylan evidently designated as their 30(b) (6) witness on
25 these topics, so those objections are overruled.

1 With that, I think we can begin with the trial.

2 I'll call first on the plaintiff if you wish to
3 have an opening statement.

4 MR. FLATTMANN: Yes, your Honor, we do. With
5 the Court's permission, I'll hand up a binder of the slides
6 we used during the opening.

7 THE COURT: And you provided those to defense I
8 assume?

9 MR. FLATTMANN: I am right now, your Honor.

10 THE COURT: Okay.

11 MR. FLATTMANN: Two copies, your Honor.

12 THE COURT: Thank you.

13 (Slides passed forward.)

14 MR. FLATTMANN: Your Honor, this case is about
15 the first orally available treatment for rosacea, Galderma's
16 Oracea product. Oracea was approved by the FDA in July of
17 2006. As your Honor heard at the preliminary injunction
18 hearing, rosacea is a disease that affects millions of
19 Americans. As you can see from this picture, patients from
20 rosacea often endure red pimple-like lesions on their faces.
21 These are known as the as the papules and pustules of
22 rosacea.

23 In 2000, Dr. Robert Ashley, the inventor of the
24 Ashley patents discovered the surprising fact that
25 sub-antimicrobial amounts of tetracycline compounds can be

1 used to effectively treat rosacea, and that revolutionized
2 the treatment of this disease.

3 Your Honor, Oracea is covered by three sets of
4 patents which are each directed to a different aspect of the
5 invention and the product here.

6 First, the two Ashley patents. Whoops.

7 First, the two Ashley patents which you heard
8 about in the preliminary injunction hearing. They cover
9 Oracea's novel method of treating the papules and pustules
10 of rosacea and reducing side effects by administering
11 doxycycline at sub-antimicrobial doses. And you will hear
12 about these patents from plaintiffs' expert dermatologist,
13 Dr. Guy Webster.

14 Second, the Chang '532 patent covers Oracea's
15 unique once daily formulation of doxycycline without
16 antibiotic effects.

17 And Oracea, as you know, is comprised of
18 30 milligrams of immediate release, or IR, doxycycline and
19 10 milligrams of delayed release, or DR, doxycycline.

20 And you are going to hear about this patent from
21 plaintiffs' formulation expert Dr. Edward Rudnic.

22 And finally the two Amin patents which you heard
23 about from the first claim construction hearing. They
24 covered Oracea's novel use of doxycycline to reduce the
25 inflammatory lesions of Oracea by inhibiting the production

1 of nitric oxide. And you will hear about those patents from
2 plaintiffs experts', Dr. Matthew Grisham and Dr. Jim Oates.

3 Let me just introduce some of these witnesses to
4 you since most of them are in the courtroom today.

5 First -- and I will ask them to stand when I
6 name them.

7 First, Dr. Guy Webster. Dr. Guy Webster is a
8 renowned clinical dermatologist and he will testify about
9 the Ashley patents.

10 Next up is Dr. Edward Rudnic. And he is one of
11 the world's leading formulation experts. And, in fact, an
12 inventor or driving force behind many of Mylan's supposedly
13 invalidating prior art references. He will testify about
14 the Chang patent.

15 Dr. Grisham is also here. He is a renowned
16 scholar in the field of molecular and cellular physiology
17 and he will tell us all about the Amin patents.

18 Dr. Oates is a renowned scholar in the field of
19 clinical rheumatology and also in the biological functions
20 of nitric oxide. He is not here today but you will hear
21 from him later in the trial concerning the Amin patents.

22 And, lastly, Dr. John Murray, who is Galderma's
23 marketing expert and economist here. And he will testify
24 about the secondary considerations of nonobviousness,
25 including the undisputed commercial success of this drug.

1 Your Honor, in the course of the trial, you will
2 hear about the problems both short term and long term that
3 have historically been associated with prescribing chronic
4 doses of antibiotics. Before Oracea, tetracycline compounds
5 were used to treat rosacea only in very high antimicrobial
6 doses, and because rosacea is a chronic condition, patients
7 were prescribed chronic courses of antibiotics as treatment
8 for the rosacea and that created two significant risks.

9 First, it created a short term risk of
10 undesirable side effects, such as phototoxicity, digestive
11 problems and others that you will hear about. And,

12 Two, it created a long term risk of antibiotic
13 resistance which is a severe public health problem and
14 concern.

15 But conventional wisdom at the time was still to
16 use greater doses for greater effect. Kill the bugs, so to
17 speak.

18 So no one considered giving a lower dose at that
19 time, let alone giving a sub-antimicrobial dose. That was
20 counterintuitive, and nobody did that until Ashley and his
21 colleagues at CollaGenex came along.

22 Now, while it was known that tetracycline
23 compounds had certain antiinflammatory properties, it wasn't
24 known that rosacea could be treated with doses that were low
25 enough to avoid these undesirable antibiotic effects but

1 still high enough to maintain efficacy. Oracea found that
2 surprising middle ground and that was counterintuitive.

3 CollaGenex basically conceived of harnessing the
4 antiinflammatory properties of tetracyclines to treat the
5 inflammatory lesions of rosacea.

6 And you can see from the figure, the subsequent
7 six month clinical trial by Skidmore that you will hear
8 about during the course of the trial showed that
9 sub-antimicrobial dosing of doxycycline significantly
10 reduced lesion count in these patients and that was the
11 basis or the discovery that was the basis for the Ashley
12 patents.

13 Now, the invention of the two Ashley patents was
14 initially tested using immediate release formulation of
15 doxycycline, administered as 20 milligrams twice a day. And
16 the Ashley patents embody and they claim those inventions.

17 And while the 20-milligram twice daily dosage
18 regime was believed to be safe and effective, there was an
19 unmet need still for a once-daily dosage of doxycycline that
20 didn't have antibiotic effect. And as you will hear, a
21 once-daily dose is especially important in treating a
22 chronic disease like rosacea because it's more convenient
23 for the patients and as a result, it increases patient
24 compliance.

25 Mylan's own asserted prior art in this case,

1 that it recently put on to its revised 282 notice tells us
2 that there was a long felt need for such a dose.

3 Okay. CollaGenex sought to work with a company
4 that specialized in dosage formulations to develop a
5 once-a-day formulation, and it's first partner was an
6 Australian company called Faulding. It completely failed to
7 come up with once daily formulation despite three tries, and
8 despite its significant experience in the formulation area.

9 Faulding's failure really highlights the
10 challenges that were inherent of developing a once daily
11 formulation of this particular drug. They couldn't make it
12 work. It always lacked enough bioavailability to be
13 efficacious.

14 However, the Chang inventors who were working at
15 Supernus, a division of Shire at the time, came along and
16 they were ultimately successful in developing the once daily
17 formulation that is Oracea today and that discovery is the
18 discovery of their patent.

19 Indeed, it was Supernus's formulation that came
20 over the once-a-day formulation challenges that were
21 presented by doxycycline. Mylan is going to tell you
22 throughout the course of the trial that the Chang patent is
23 invalid because the Chang inventors supposedly derived their
24 invention through CollaGenex, but according to Robert
25 Ashley, who was CollaGenex's vice president at the time,

1 CollaGenex just didn't come up with this particular
2 invention of Chang. CollaGenex didn't have the expertise to
3 formulate a once-daily doxycycline as claimed in the Chang
4 patent. It was Supernus and the Chang inventors that
5 finally pulled that off.

6 Now, while it was surprising that rosacea could
7 be effectively treated with sub-antimicrobial dose of
8 doxycycline that was administered once daily, one of the
9 antiinflammatory uses by which Oracea works was the subject
10 of an unexpected and surprising discovery. Specifically,
11 researchers at the State University of New York and at NYU
12 discovered that tetracyclines, including doxycycline, could
13 be used to reduce the production of nitric oxide by
14 inhibiting expression of inducible nitric oxide synthase,
15 which is the enzyme that makes nitric oxide. And, in
16 particular, the inventors realized that tetracyclines could
17 be effective in treating chronic inflammatory diseases
18 mediated by inducible nitric oxide synthase, and that novel
19 use of tetracycline compounds to reduce the production of
20 nitric oxide was the basis for the Amin patents.

21 Now, you will be hearing about all three of
22 these sets of patents in the case, your Honor. And each
23 represents a distinct aspect of the inventions covering the
24 novel drug Oracea. Each patient is listed by Galderma in
25 the FDA's Orange Book. Each patent is important to the

1 success of this product and, tellingly, even though Mylan
2 already markets a 50-milligram antibiotic doxycycline drug,
3 Mylan wants to market this 40-milligram once-a-day
4 sub-antibiotic drug and make a generic copy of Oracea.

5 If Oracea isn't novel, then why would Mylan want
6 to take the time and experience to market a generic version
7 of it when it already has a 50 milligram drug on the market?
8 And I think that is telling.

9 The issues to be tried, there are only two:

10 Whether Mylan infringes the asserted claims of
11 the Ashley and Amin patents and two dependent claims of the
12 Chang patent. And,

13 Second, whether Mylan has proven by clear and
14 convincing evidence whether it can meet that high burden of
15 proving that the asserted claims of these three patents, all
16 of them, are anticipated or obvious.

17 Let's take infringement first.

18 Here, your Honor, Mylan infringes all three sets
19 of patents at issue, and you will hear evidence proving
20 that. In fact, it's not even clear what noninfringement
21 defenses Mylan has left at this stage.

22 First, the Chang patent. Mylan has already
23 conceded infringing numerous claims of the Chang patent. As
24 per the stipulation that was signed by your Honor, Mylan is
25 not asserting noninfringement of claims 1 to 3, 5, 7 to 9,

1 13 to 17, or 19 to 21 of the Chang patent. Nor could it.
2 It copied the formulation.

3 Now, only one -- only asserted claims 4 and 18
4 remains in terms of the question of infringement, but the
5 evidence is clear that Mylan infringes both of them. As you
6 can see from the claim language here, the relevant language
7 concerning whether Mylan infringes is whether it falls
8 between the steady state blood levels of .3 microgram per
9 mil to .8 microgram per mil. Your Honor heard about that.
10 In fact, it was a central issue in the last Markman hearing.
11 And the clinical data will show that patients taking Mylan's
12 drug will definitely meet those blood levels.

13 Mylan relies on CollaGenex's pharmacokinetic
14 studies in its proposed ANDA and package insert. Those
15 studies tell us that Mylan's patients will have steady state
16 plasma concentrations between .3 and .8 micrograms per ml.
17 That is all that is required for infringement of these
18 dependent claims.

19 You are going to also hear from Galderma's
20 formulation expert, Dr. Rudnic, who is one of the most
21 successful formulators in the industry, and he is going to
22 testify that patients taking a once-daily Oracea doxycycline
23 formulation will fall within this range.

24 But it is better than that. Mylan has already
25 admitted infringement of these claims on multiple occasions

1 before this Court. Going back all, all the way back to the
2 preliminary injunction hearing last May, Mylan's counsel
3 acknowledged that the parties agree that Mylan doxycycline
4 concentration value achieved in the patient is .6 micrograms
5 per milliliter. .6, right in the middle of the range.

6 And that position has been unwavering and has
7 not changed. As recently as a few weeks ago, in its portion
8 of the pretrial order, Mylan acknowledged that the mean
9 trough -- that means the low part, C_{min} -- of the doxycycline
10 serum concentration of Mylan's proposed ANDA product is .3
11 micrograms per ml.

12 If that is the bottom number for Mylan's
13 patients, they fall within the range. They certainly do.
14 So I don't see how Mylan can now dispute this at trial.
15 Mylan should concede infringement right now and not put us
16 to our proofs. But if it does, we will make them.

17 Now, as to Ashley, the Ashley patents, this
18 Court already preliminarily found a strong likelihood that
19 Mylan infringed these patents. And all Mylan has done to
20 date is repeat its old in vitro arguments, namely, reliance
21 on in vitro evidence in an attempt to show non-infringement
22 of claims about an in vivo drug.

23 This Court rejected those arguments once and I
24 submit it should do so again after hearing the evidence.

25 This sub-antibacterial amount that we are

1 looking at in the Ashley patents is an in vivo amount. That
2 is not surprising. The whole point of these inventions is
3 that they are administered to human beings, not test tubes.

4 Now, Your Honor, again, the focus will be on
5 these sub-antibacterial amount limitations that Your Honor
6 has defined in the Markman hearing. And Your Honor defined
7 that term as a lack of significant inhibition or growth of
8 microorganisms, for example, bacteria.

9 If we look at Mylan's label again -- we will in
10 the course of the trial -- we will see it reads directly on
11 that claim limitation. Mylan's label says that it
12 demonstrated no detectable long-term effects on bacterial
13 flora, that it shouldn't be used for eliminating bacterial
14 disease.

15 It says it shouldn't be used for eliminating any
16 microorganism. It says do not treat infections with this
17 drug.

18 That is directly in contradiction to Mylan's
19 litigation position. The contrast is remarkable. The label
20 says, Should not be used for eliminating microorganisms.
21 The litigation position is that it will significantly
22 inhibit the growth of many of the identified pathogens.

23 The label says do not treat infections caused by
24 bacteria. The litigation position of Mylan is that it will
25 significantly inhibit the growth of microorganisms.

1 It goes on, the label says there is no
2 detectable long-term effect on bacterial flora. Mylan will
3 tell you today that there is not evidence that it will not
4 significantly inhibit the growth of any microorganisms that
5 reside in the nose, throat, lungs or eyes.

6 So Mylan's positions are directly contradicted
7 by its label.

8 You will also hear their testimony through Dr.
9 Talton that Mylan has no evidence that its drug inhibits
10 microorganisms, and has no information contradicting the
11 statements in the label. It has already admitted before
12 this Court that the statements in the label are true.

13 Let's move on to the Amin patents.

14 Mylan and its experts are going to fail to rebut
15 infringement of the Amin patents.

16 You will hear from Galderma's expert in this
17 field, Dr. Grisham. He will testify that the use of Mylan's
18 ANDA product in accordance with Mylan's label will inhibit
19 the production of nitric oxide synthase as per the claims,
20 and will do so by inhibiting inducible nitric oxide synthase
21 in a way that infringes the patent. Specifically, he will
22 testify that the production of nitric oxide and inducible
23 nitric oxide synthase to a number of effects, vasodilation,
24 erythema, increased vascular permeability, leukocyte
25 invasion and edema, which are the causes of the signs and

1 symptoms of rosacea, including the papules and pustules of
2 rosacea. And he will tie these inextricably together with
3 the administration of Mylan's product.

4 Mylan's expert, Dr. Robbins, is not going to
5 contest the basic facts on this. He is not going to contest
6 that the production of nitric oxide and inducible nitric
7 oxide synthase will lead to the effects I have just
8 described.

9 They are not going to contest that the use of
10 doxycycline decreases the effects of nitric oxide or nitric
11 oxide synthase, and they simply can't dispute these basic
12 facts in order to overcome our proof of infringement by a
13 preponderance of the evidence.

14 Indeed, you will see that Dr. Robbins's own
15 work, that Dr. Robbins will show that doxycycline inhibits
16 nitric oxide and inducible nitric oxide synthase. And if he
17 testifies in a manner consistent with his deposition, he
18 will admit that as well, because it is right in his
19 deposition.

20 As Your Honor can see, it will be clear that
21 Mylan infringes all three sets of patents. Mylan already
22 agrees that it infringes most of the claims of the Chang
23 patent. And the evidence will show that it infringes the
24 other patent claims as well.

25 Now, Mylan will fare no better on its invalidity

1 defenses. That is because as to all three of these sets of
2 patents, Ashley, Chang and Amin, Mylan's proofs fall short
3 of its heavy burden of showing invalidity by clear and
4 convincing evidence.

5 Now, Mylan cites dozens of references, piles of
6 art, against all three patents. To my dismay, that hasn't
7 changed since I brought up the issue before the Court at the
8 pretrial conference.

9 It raises these piles of art against all three
10 of the patents. It won't be able to present any argument
11 that comes close to disclosing all the elements of the
12 asserted claims that are making these claims obvious. In
13 fact, the citation of this voluminous collection, this
14 kitchen-sink-full of art, begs the question. Now, if the
15 inventions have been so obvious for so long and in view of
16 so many references, why didn't anybody else do it first?
17 And why does Mylan need so many references to invalidate
18 these patently obvious claims? Because they are not.

19 No matter how many references Mylan relies on or
20 tries to stack up against Galderma's patents, the results
21 are going to be the same, they just don't support the
22 arguments.

23 Now, Mylan has retooled and re-jiggered these
24 piles of art in the last couple of weeks, more than once,
25 and it has dropped some of the art, three pieces of art

1 against Ashley and two against the others. Those are gone.

2 It has added other art. But the new
3 combinations still don't come close to disclosing the
4 elements of the claim or making them obvious. And I will
5 take you through them and the evidence that we will be
6 presenting.

7 As Your Honor saw from the previous slide, Mylan
8 is now relying on 15 references in its attempt to invalidate
9 the Ashley patents alone. We will take a closer look at
10 them.

11 First, Mylan won't even try to show that any one
12 of the nine Gilchrest references as we referred to them at
13 the PI hearing disclose all the elements of any of the
14 asserted claims.

15 They are up on Slide 35 here.

16 Perhaps realizing the shortcomings of these
17 references, Mylan has recently dropped three of them
18 entirely, and I have crossed them out on the slide. So we
19 are down to six. Here is a timeline of the now six
20 Gilchrest references that Mylan relies on. Note the lengthy
21 period of time between these references and the Ashley
22 patent filing: decades. They were all published decades
23 before the Ashley patents were even filed. If the Ashley
24 patent was so obvious, why didn't someone rely on this
25 reference to make this invention 30 years earlier or even 40

1 years earlier when the Murphy article was first published?
2 It's because it didn't teach anything. It didn't teach
3 antimicrobial amount.

4 They suffer from critical failures. They have
5 no disclosure of doxycycline at all. They have no
6 disclosure of a treatment of rosacea with a
7 sub-antibacterial amount of doxycycline. They contain no
8 disclosure of any dose of any antibiotic under a hundred
9 milligrams a day. And they contain no disclosure whatsoever
10 of any failure or non-reduction in bacterial flora.

11 You will hear from Galderma's expert, Dr.
12 Webster, who will point out these deficiencies in each of
13 the six Gilchrest references and show why they fall short of
14 anticipating the claims.

15 If Dr. Gilchrest, Mylan's expert, testifies
16 consistent with her deposition in this case, she will have
17 to admit that these references fall short. For instance,
18 she will have to admit that none of the references disclose
19 tetracycline administered in an amount that is
20 sub-antibacterial.

21 She will have to admit that none of them
22 disclose that they failed to inhibit the growth of
23 microorganisms. She will have to admit that none of them
24 disclose anything lower than a hundred milligrams a day of
25 any antibiotic or any non-reduction of skin microflora.

1 Those are critical failures in Mylan's case.

2 These references should have been dropped in
3 view of these admissions.

4 Now, Mylan primarily relies on that collection
5 of references as far as we can glean from the 282 statement.

6 But it also continues to rely on the Pflugfelder
7 patent, which the PTO considered to be the closest prior art
8 to Ashley. But the patents issued over Pflugfelder anyway
9 because, as the patent examiner recognized, Pflugfelder did
10 not teach methods for treating papules and pustules of
11 rosacea by administering tetracycline in an amount ten to 80
12 percent of the antibiotic effective amount with no reduction
13 of skin microflora. So it basically recognized the failure
14 of that art.

15 But Mylan is stubbornly pushing forward with the
16 Pflugfelder references, as far as I can tell.

17 Indeed, Mylan's expert admitted during her
18 deposition that she doesn't consider the Pflugfelder
19 reference as anticipatory art against the Ashley patents but
20 only as one of many other references she uses to support her
21 obviousness argument.

22 Your Honor, as I mentioned a few times, Mylan
23 has recently added five new references and even more distant
24 references to support its invalidity references against
25 Ashley. Now, all those these references were cited long ago

1 in one of Mylan's interrogatories where it listed hundreds
2 of references. They only recently resurfaced in the last
3 two weeks. And adding more art to the pile at the last
4 minute is not going to help Mylan meets its burden because
5 none of these new references are any better in teaching the
6 limitations of the claim. They're even more distant. None
7 of them discloses the use of sub-antibacterial amounts of
8 doxycycline to treat rosacea, and that is clear on their
9 face.

10 The first two are formulation patents using
11 antibiotic amounts of tetracyclines. That's the Muhammad
12 and Doyon patents. The next two, the Hussar and Pechere
13 articles are just articles of patient compliance. They
14 don't teach the claims of this invention and Maibach is
15 about using an antibiotic amount of doxycycline hyolate. So
16 they're even more distant.

17 Mylan has continuously reshuffled its references
18 from Day One, and I think that is very telling. These are
19 the five references that Mylan relied on in its paragraph 4
20 notice stating its intention to make a generic copy of
21 rosacea. And since that time, only one reference has
22 survived Mylan's reshuffling. The Pflugfelder reference.
23 That's the only common denominator. And Mylan has stacked
24 all of these additional references on top of it in order to
25 try to make its case.

1 Let's talk a little bit about Mylan's
2 Dr. Feldman defense. And I call it Mylan's Dr. Feldman
3 defense because I will submit it's not a public use defense
4 because they can't prove it was public at all.

5 You recall that following the PI hearing, Mylan
6 moved the Court to reconsider its decision based on the
7 alleged private use of Periostat by a single physician,
8 Dr. Lawrence Feldman. And it seemed they considered
9 Dr. Feldman to be a centerpiece of its reshuffling at that
10 time. At least us. But now Dr. Feldman will not even be
11 appearing live in this court.

12 In any event, you will hearing by deposition
13 designation that Dr. Feldman claims that he used Periostat
14 personally and that he administered it to a patient, and
15 these alleged uses will fail to invalidate the Ashley
16 patents on multiple grounds.

17 To put it simply, at most there is
18 uncorroborated private use, if a use at all, if they even
19 have it and it doesn't count as prior art under the law, and
20 it wasn't known to anyone in the U.S.

21 The overwhelming evidence from Dr. Feldman
22 himself and the lack of evidence as you will see from his
23 deposition will show that it was unpublished, undisclosed,
24 unappreciated, uncorroborated and undeveloped, your Honor.

25 It was never made public. It was never reduced

1 to practice. It was never commercialized.

2 Given the supposed importance of Dr. Feldman's
3 testimony to Mylan's defense, I think it's telling that
4 they decided not to put him on the stand. It's not too
5 surprising I guess given his use was uncorroborated by
6 anyone, and it won't be corroborated by anyone else here at
7 trial. And such uncorroborated testimony of a supposed
8 prior art use isn't legally relevant and should rightfully
9 either be excluded or ignored by the Court. Certainly,
10 given very little weight.

11 Even if such testimony is considered by the
12 Court, it will show that his alleged uses were private,
13 uncorroborated and irrelevant.

14 He testified that he didn't tell any
15 dermatologist that he used Periostat to treat rosacea. He
16 didn't discuss it with anyone. He never wrote anything
17 about it. He never attempted to sell the idea. He never
18 called CollaGenex about it. He never submitted a patent
19 application. There is simply no evidence that he even
20 prescribed Periostat to a single patient to treat rosacea.

21 No one has even seen this alleged prescription.
22 We don't know if the use ever happened. And, more
23 importantly, neither does Dr. Feldman because he doesn't
24 know if the patient filled the prescription according to his
25 deposition. He doesn't know if the patient even took the

1 drug if she did fill the prescription. He doesn't know if
2 the patient was successful in clearing up her rosacea. He
3 didn't even have a follow-up visit with the patient. Not
4 for another four years. The rosacea didn't come up.

5 That can't satisfy a clear and convincing
6 burden.

7 Now, as your Honor can see, even one of Mylan's
8 new references that it added last week, the Hussar paper,
9 citing no less than Hippocrates himself, the father of
10 Western medicine, as an authority, casting doubt on whether
11 this ever happened, cautioning, "keep watch also on the
12 fault of patients which often makes them lie about the
13 taking of things prescribed."

14 We have a right to be cynical of this use
15 because no one can prove it ever happened.

16 Mylan's expert on this point, Dr. Gilchrest,
17 also admitted in her deposition that she doesn't know if
18 Dr. Feldman's patient ever took the Periostat. And I think
19 that was a fair answer. None of us know.

20 More importantly, Dr. Gilchrest is not aware of
21 anyone who prescribed a dose of less than 50 milligrams of
22 doxycycline, which is an antibiotic dose, for the treatment
23 of rosacea prior to April of 2001.

24 Now, given her expertise, and her prominence in
25 this field over many decades, if anyone would have known,

1 she would have known.

2 Dr. Stafford, who is Mylan's expert on IMS data,
3 admitted it is impossible to directly link the patient who
4 is allegedly prescribed Periostat with the patient who later
5 filled a Periostat prescription with IMS data. And that is
6 for good reason. IMS removes all patient identifying
7 information from your data, and IMS does not report the
8 condition for which drugs are prescribed. So as
9 Dr. Stafford testified, he can't use the IMS data to link to
10 prescriptions of any particular patients, including this
11 alleged patient.

12 Dr. Stafford also admitted that he doesn't know
13 a single dermatologist prior to April of 2000 who prescribed
14 Periostat off-label. He couldn't name one.

15 So, in summary, Mylan's speculation about Dr.
16 Feldman's prior uses will amount to a colossal failure of
17 proof.

18 Let's move on to Mylan's invalidity arguments
19 concerning the Chang patent. It cites over 16 references
20 against the Chang patent, but it won't be able to present
21 any art that comes close to disclosing all of the elements
22 of the asserted claims when making those claims obvious.

23 There are two sets of art that Mylan argues are
24 the closest prior art here, and Mylan's expert argues are
25 the closest prior art here: The Ashley patent applications,

1 and the Ashley method-of-use patents that are in suit here.

2 But those so-called closest prior art references
3 don't disclose a single specific once-a-day dosage form of
4 doxycycline of any type. No actual formulation, much less
5 the required immediate release, delayed release formulation
6 of the Chang patent claims. So Mylan asks this Court to
7 invalidate a formulation patent based on references that
8 don't even disclose an actual formulation.

9 Aside from these closest prior art references,
10 Mylan falls back on a full deck of more distant art for its
11 invalidity defense, but one has to ask, if Mylan's closest
12 art fails to establish invalidity by clear and convincing
13 evidence, how can the more distant art fare any better?

14 You will hear from Dr. Rudnic as to why none of
15 these prior art references invalidates the Chang patent. He
16 is in a unique position to testify here because he is the
17 inventor of the Rudnic patent publication that was cited as
18 the closest prior art to Chang by the Patent Office. He is
19 also the inventor of other prior art patents and
20 formulations upon which Mylan relies.

21 He will testify that he finds the Chang patent
22 invention counterintuitive, novel, and nonobvious. He is in
23 a unique position to assess that.

24 Let's take a closer look at some of the art. As
25 I said, the Ashley patent applications don't disclose actual

1 formulations. Certainly, not formulations of immediate
2 release, delayed release components.

3 In fact, they teach away from the invention
4 here because they talk about a release over 6 to 12 hours,
5 so-called sustained release over that period, whereas that
6 is not what the Chang patent concerns, and you will hear
7 about that from Dr. Rudnic.

8 The Ashley patents that are in suit here also
9 won't save Mylan's case because they don't disclose any
10 actual examples of any once-daily formulations, much less
11 the ones that have been claimed. Much less delayed release
12 portions of Chang.

13 Mylan says that Ashley invented the Chang patent
14 formulations, but Ashley testifies to the opposite. You
15 will hear that in his designated testimony. He says he
16 didn't know how to develop those formulations. He testified
17 that his unissued applications and his patents in suit here
18 simply don't disclose the formulations.

19 Now, amazingly, and I don't understand how this
20 remained on their 282 list, Mylan argues that the three
21 Periostat references anticipate Chang. I didn't say render
22 obvious but anticipate. Well, Periostat is not even a
23 once-a-day formulation.

24 Dr. Friend cites further in his report -- he is
25 their formulation expert -- cites more distant references in

1 support of his claim that the Chang patent is anticipated,
2 but if he testifies consistent with his deposition, he will
3 have to admit that none of these references expressly
4 discloses a formulation with 30 milligrams of immediate
5 release and 10 milligrams of delayed release. They simply
6 don't disclose that 75 to 25 ratio.

7 They admitted it with regard to the Sheth patent
8 at his deposition here. He admitted it to the Ashley method
9 of use patents, Swintosky and the Ashley patent applications
10 and the Rudnic application and the Periostat references and
11 something that is not even prior art, the Ashley 2002 slide
12 deck. He admitted that with regard to every piece of the
13 prior art, that it didn't contain the fundamental element of
14 the claims.

15 So he will also admit Dr. Feldman's alleged use
16 of Periostat, which is somehow asserted against the Chang
17 patents as well, does not anticipate or render obvious the
18 Chang patent.

19 The fact of the matter is that people just
20 hadn't tried to make once daily sub-antibacterial oral
21 drugs. The whole history of once-a-day administration of
22 antibiotics focused on high antimicrobial doses. Just like
23 Ashley, this is new.

24 By reporting to the PTO, as I said, the closest
25 prior art was Dr. Rudnic's patent publication. But the PTO

1 issued the Chang patent publication over the Rudnic
2 application, citing the 40-milligram dose in Chang. He had
3 recognized the difference.

4 In fact, it stated that the Rudnic application
5 does not teach or fairly suggest an oral pharmaceutical
6 composition of doxycycline as disclosed in the claims. Nor
7 does it teach or fairly suggest dosage forms of this kind.

8 You will hear Dr. Rudnic himself explain how his
9 invention was different from the Chang patent, and how the
10 Chang claims are novel, nonobvious and counterintuitive.

11 Now, the other kitchen sink full of art that
12 Mylan relies on is related to different active ingredients
13 like amphetamines, different pharmacokinetic parameters,
14 different approaches to the PK profile that you see in
15 Chang, and completely different effects, antibacterial
16 effects, the opposite of this invention.

17 Mylan takes all of these pieces of art and
18 argues that individual elements were there in the art but
19 never shows that anybody combined them, that the combination
20 would have been obvious at the time of invention.

21 Instead, in hindsight, what Mylan will be doing
22 is cherry-picking various pieces from each of these dozens
23 of references and dozens of sources and cobbling them
24 together as if the Chang patent formulation and invention
25 was already known and in hand, and that is an improper way

1 to approach obviousness.

2 Let's move on to the Amin patent, the third
3 file.

4 Mylan once again cites over eight references
5 against the Amin patents. However, it hasn't identified any
6 invalidating art. In fact, it dropped the only two
7 references that it allegedly was relying on to support its
8 obviousness defense. All the other references it has
9 asserted only as anticipatory.

10 So it's left to argue anticipation of the Amin
11 patent with eight references that don't even mention nitric
12 oxide.

13 These are the eight references that Mylan cites.
14 Five of these references are from two of the inventors of
15 the Amin patents. That's the Golub and Greenwald
16 references. But by Mylan's own experts admission, none of
17 the eight Robbins references they cite expressly or
18 inherently disclose nitric oxide inducible nitric oxide
19 synthase in claimed amounts. And I will show you that.

20 Mylan's expert, Dr. Robbins admitted, and he
21 will do so again, if he testifies consistent with his
22 deposition, that the Amin patents were the first disclosure
23 of tetracycline inhibiting nitro oxide or inducible nitric
24 oxide synthase. And that is an express admission that these
25 patents are novel. None of the art that came before even

1 came close.

2 And as Mylan has dropped its obviousness defense
3 and its own expert admitted novelty, it can't quite prove
4 its defense.

5 The additional references that are identified by
6 Mylan are even more distant. None discloses the inhibition
7 of nitric oxide, as I said. Periostat they raised, but
8 Periostat isn't a reference because it wasn't available
9 until 1998 and that critical date of the Amin patents
10 earlier.

11 It waves its hand about some early clinical
12 testing of Periostat, but it doesn't provide evidence of
13 that or show it represented prior art. And it was just
14 early nonpublic work by the drug sponsors or the inventors.

15 And Galderma's expert, Dr. Rose will further
16 confirm a person of ordinary skill will not have reasonably
17 expected at the time that tetracyclines could be used to
18 inhibit inducible or nitric oxide synthase expression and
19 nitric oxide production in humans or that tetracyclines that
20 have substantially no antimicrobial activity could be used
21 for that purpose.

22 Your Honor, the common sense objective
23 indicators of nonobviousness also point strongly in the same
24 direction to validity here.

25 I would once again like to note Mylan dropped

1 its obviousness defense to the Amin patents because it dropped
2 any of the arguments it is relying on for obviousness, and
3 Mylan never put in an expert report in rebutting the
4 commercial success of Oracea based on the Chang formulations
5 so this question will become a fairly narrow one.

6 First, unexpected results. The results
7 obtained by these inventions were entirely unexpected.
8 Sub-antibiotic amounts worked to treat rosacea. Nobody knew
9 that. Nobody expected that. It was the opposite of what
10 doctors believed.

11 Rosacea was thought by many to be bacterial in
12 nature and was treated with antibiotic dosages by everyone,
13 including Dr. Gilchrest. It was completely counterintuitive
14 that sub-antibacterial amounts would work.

15 Once daily dosing works for sub-antibiotic
16 amounts of doxycycline. Nobody knew that either.

17 No one thought these levels, these blood levels
18 could be obtained with an antibiotic in a once daily dose or
19 that they would work.

20 Substantially no side effects. This is
21 something that is great for patients and it didn't exist
22 before Oracea. The drug exhibits no phototoxicity, so it so
23 they can enjoy the drug during summer. It decreases
24 antibiotic resistance problems that occurred and were a
25 public health menace, and it doesn't cause gastrointestinal

1 disorders and other side effects.

2 We will point to the failure of others,

3 particularly with regard to the Chang patents.

4 Faulding, a sophisticated a company, a go-to company, they
5 failed three times to make this.

6 Long felt need. As you will hear from

7 Dr. Webster, there was a need for a safe and effective oral
8 treatment for rosacea. It's worth mentioning, and you will
9 hear it again in Dr. Webster's testimony, this was the very
10 first FDA approved oral treatment of rosacea in a
11 sub-antimicrobial amount.

12 Even today it's the only orally available
13 treatment for rosacea, FDA approved.

14 The need for once-daily forms also was clear,
15 even Mylan's own Hussar prior art shows that patient
16 compliance was an issue and once-a-day formulations improved
17 that. And there was a need for a safe and effective
18 treatment of rosacea because long-term administration of
19 antibiotics were known to cause side effects.

20 Finally, the asserted claims of the three sets
21 of patents all cover Oracea, as you will hear from
22 Galderma's experts who conducted those analyses.

23 And Galderma's significant annual sales
24 demonstrate the commercial success of the product.

25 Since launch in 2006, those sales have been over

1 \$290 million in gross sales, in fiscal year 2010 alone.
2 Prescriptions have grown steadily since the launch in July
3 of 2006. You will hear all this from Dr. Murray. And there
4 is a clear nexus between Oracea's unique patents and
5 Oracea's commercial success, and Dr. Murray will explain how
6 this relates to each of these patents. That nexus between
7 the Chang patent and commercial success will not be refuted.
8 In fact, before the Chang patent was issued in the case Dr.
9 Nelson's deposition was taken. He is their commercial
10 success expert. And he admitted at that deposition that
11 there would be a link between the sale of Oracea and any
12 patents covering Oracea's once-a-day formulation.

13 That is precisely what the Chang patent claims.
14 Now that the Chang patent is at issue, Dr. Nelson will have
15 to concede this again if he testifies consistent with that
16 deposition testimony.

17 Now, finally, even Mylan's other experts have
18 admitted Oracea is a commercially successful product.

19 Your Honor, in conclusion, the evidence will
20 show that Mylan infringes each of the patents in suit here.
21 And it also will show that their invalidity defenses will
22 fall short. They are forced to cobble together dozens of
23 references in Byzantine combinations just to make a
24 nonobvious assertion. But none of them disclosed the
25 invention. Despite the piles of prior art, nobody disclosed

1 this invention for decades. The alleged Feldman prior uses
2 are not corroborated at all. They were uncorroborated then,
3 they are uncorroborated today. They won't be corroborated
4 in this court. And Dr. Feldman is not here to shed any
5 light on this matter.

6 Common-sense factors will further confirm the
7 validity of these patents, Your Honor.

8 Thank you very much.

9 THE COURT: Thank you very much. We will hear
10 from Mylan if you wish to make an opening.

11 MR. STEUER: Thank you, Your Honor.

12 Good morning, Your Honor. Dave Steuer for
13 Mylan.

14 I have some books.

15 THE COURT: You may approach, and good morning
16 to you.

17 MR. STEUER: Your Honor, this is a case
18 involving five patents. We call two of them the Ashley
19 patents, two of them the Amin patents, and one of them the
20 Chang patent. We are here to discuss whether these patents
21 may serve to prevent Mylan from selling its FDA approved
22 ANDA product. The evidence will show ultimately that they
23 may not.

24 Here in short is what we will offer as evidence
25 and prove in this trial. We will show that the Ashley

1 patents are not infringed by Mylan's patents. We are not
2 relying solely on in vitro evidence but in fact in vivo
3 evidence. Definitive in vivo evidence will show a
4 significant antibiotic effect caused by the Mylan ANDA
5 product.

6 We will show that it is invalid. It was
7 anticipated by the public use of Dr. Feldman. It is
8 anticipated by the prior art. It is obvious.

9 With respect to the Amin patents, we will show
10 the Court that there is no evidence that 40 milligrams of
11 doxycycline has any effect in decreasing nitric oxide
12 synthase or inducible nitric oxide synthase -- excuse me,
13 decreasing nitric oxide.

14 And there is no link between an increased nitric
15 oxide and inducible nitric oxide synthase, or iNOS, and the
16 papules and pustules of rosacea.

17 With respect to invalidity, because this is an
18 inherent property of doxycycline, claims the inventors, it
19 is an inherent property that appeared in prior use of the
20 product of doxycycline formulations and thus was anticipated
21 by use as an inherent property and is non-enabled by the
22 patent in any event.

23 With respect to the Chang patent, we will show
24 the patents are invalid. They are anticipated by the Ashley
25 patent applications, which is not surprising since Ashley

1 was involved in directing this formulation work.

2 The formulations were obvious, and they were
3 not -- this formulation was, in fact, not invented by the
4 named inventors and is invalid for that reason as well.

5 We will show that we do not infringe Claims 4
6 and 18. 4 and 18 require that a steady state blood level be
7 found within a specific range of doxycycline blood values.
8 There is no evidence, they will be unable to prove that, in
9 fact, at steady state the patients stay within, that is
10 between the range that has been specified by the Court.

11 So to summarize as to the Ashley patents, there
12 is no infringement.

13 The Amin patents, there is no infringement. The
14 Chang patent, we will give evidence that there is no
15 infringement as to two claims. We concede the infringement
16 as to the other claims because essentially the Chang patent
17 is what is called a picture claim, which basically just
18 describes the product.

19 But 4 and 18 are not infringed. And as to all
20 of them we will present the Court with clear and convincing
21 evidence that they are, in fact, invalid.

22 Your Honor, I want to start with the background
23 to these inventions, which we didn't hear about much in
24 Galderma's opening, because the background is very important
25 to show the abundance of knowledge about rosacea acne and

1 about the prior art regarding low dose use of tetracycline,
2 including, doxycycline, for the treatment of acne rosacea.

3 First of all, it should be pointed out that
4 doxycycline in the world of antibiotics is an extremely old
5 drug when one considers that penicillin was only first
6 available in the 1940s commercially. This is a drug that
7 was first approved in 1967. It was developed by Pfizer.
8 And it was what they call a second generation tetracycline.

9 So it is an old drug. It is generic. It comes in many
10 forms, including 50-milligram capsules generic, which we
11 have there in this slide. And it's actually labeled for use
12 in acne rosacea. This is a label we see from the
13 Vibramycin. Vibramycin was the first branded doxycycline.
14 This is Pfizer's product of doxycycline. And it's labeled
15 by the FDA as useful for instructive therapy.

16 So it has been used for acne rosacea, it's
17 actually labeled for it. More than just the existence of
18 this drug, as you would expect for a drug that is almost 50
19 years old, quite a bit is known about it.

20 For example, in 1988, Saiven and Houin filed a
21 reference that tells us all about the half-life of
22 doxycycline. It tells us where absorption occurs. And
23 actually, the half-life knowledge is even older. This is
24 from 1966. It tells us what the half-life is of
25 doxycycline. That's how long it remains in the system.

1 The point of that is, because of the half-life,
2 as they knew in '66 before the drug was even approved by the
3 FDA, it makes it suitable for once-a-day administration.

4 It has also been known for almost half a century
5 that low doses of the tetracyclines are useful for the
6 treatment of acne. As Murphy said in 1962, there is
7 evidence that long-term use of tetracycline in small doses
8 combined with a traditional program of management is useful
9 and economical.

10 So this was actually known shortly after Mr.
11 Ashley was born. So it's not surprising in light of this
12 old drug and the wealth of knowledge that is known about it
13 that there is little room for true novelty in the use of
14 this old drug for an old therapeutic indication that has
15 been used by dermatologists for decades.

16 Let me turn first to briefly discuss the Ashley
17 patents.

18 In general, the Ashley patents claim a method of
19 treatment of patients who have acne, including acne and
20 rosacea. Your Honor, we should point out since the time of
21 the application for PI, Mylan has benefited from discovery
22 and the Court's findings and conclusions as expressed in the
23 memorandum opinion, and our evidence on the Ashley patents
24 will frankly be quite different from what the Court
25 encountered at the preliminary injunction hearing.

1 We will provide what we believe to be compelling
2 evidence of both the invalidity of the Ashley patents and
3 non-infringement, invalidity will be shown by Dr. Feldman's
4 use, and it will be shown by the prior art.

5 With respect to non-infringement, we will
6 present to the Court in vivo evidence showing significant
7 inhibition of bacteria by 40 milligrams of doxycycline.

8 In particular, we will prove by clear and
9 convincing evidence that the Ashley patents were
10 anticipated, were obvious, based on knowledge widely
11 available to persons of skill in the art for doxycycline and
12 tetracyclines for acne rosacea, well prior to the creation
13 of the Ashley patents.

14 We will show that Periostat, a 20-milligram
15 doxycycline product, was used by a practicing dermatologist,
16 Dr. Lawrence Feldman, prior to the patent in exactly the
17 manner set out in the patents to treat rosacea, both his own
18 and his patients'. He used low-dose doxycycline to treat
19 rosacea as specified in the patents.

20 In fact, it is the preferred embodiment of the
21 patents. We will show that Dr. Feldman's records for his
22 patients corroborates his use and his patients' use. As he
23 says here, We will use Periostat 20 milligrams B.I.D., twice
24 a day, due to its anti-inflammatory effect with low risk
25 side effects. Right in that little note he describes the

1 essence of the Ashley patents.

2 Additionally, we will produce pharmacy
3 prescription evidence that shows that not only did Dr.
4 Feldman prescribe Periostat but other dermatologists
5 prescribed Periostat. Periostat, which is the original drug
6 and Oracea as a product extension of Periostat was indicated
7 for periodontal disease. Somebody doesn't treat periodontal
8 disease, they treat acne, they treat rosacea. And they
9 would not treat an infection with 40 milligrams of
10 doxycycline.

11 You heard Mr. Flattmann comment that the Feldman
12 prior uses will not be corroborated. The evidence will
13 actually show abundant corroboration. It will show that the
14 patient record created by Dr. Feldman corroborates not only
15 his but his patients' prior use of Periostat to treat
16 rosacea.

17 Dr. Feldman will testify that several of his
18 written statements on the patient record were based on his
19 prior successful use of Periostat to treat his own rosacea
20 and medical knowledge he gained from other sources,
21 regarding off-label use of Periostat, to treat rosacea.

22 In Dr. Feldman's own words, Based on my own
23 personal usage, as well as the fact that rosacea is an
24 inflammatory skin condition, I anticipated that the
25 Periostat would make her skin better, referring to his

1 patient.

2 Dr. Feldman's use proves not only anticipation
3 but also the obviousness of the invention. Indeed, for Dr.
4 Feldman, the invention was literally as obvious as the nose
5 on his face.

6 But obviousness and anticipation will also be
7 proven by the wealth of study that long preceded the Ashley
8 patents.

9 Now, with respect to infringement, all claims in
10 the Ashley patents are limited to an amount of a
11 tetracycline compound that does not significantly inhibit
12 the growth of microorganisms, any microorganisms anywhere in
13 the body, and this is the Court's construction of that term,
14 and both of them feature the requirement that they not
15 significantly inhibit the growth of microorganisms.

16 Your Honor, we will present new *in vivo*
17 evidence, that is new to the Court, the 2008 Haffajee study,
18 which shows conclusively that a 40-milligram daily dose of
19 doxycycline significantly inhibits the growth of
20 microorganisms.

21 Their researchers from the Haffajee study are
22 from the Foresight Institute in Boston which is affiliated
23 with the Harvard Dental and Medical Schools. This study was
24 not sponsored by Galderma or any other drug company. And
25 Haffajee administered 40-milligram doses of Periostat, which

1 is the preferred, especially preferred embodiment of the
2 Ashley patents, to study participants and sample for
3 microorganisms. Here is what they found.

4 I will not go through this. I will let Dr.
5 Chambers do the heavy lifting on this. What it shows is a
6 spike in the percentage of resistant organisms that occurs
7 during the administration of Periostat. So the red button
8 on top is Periostat, the pink button on the bottom is the
9 placebo. After the administration of doxycycline the spike
10 goes down.

11 But what Dr. Chambers will discuss is that the
12 spike in the percentage of resistant organisms does not
13 occur absent significant inhibition of growth. That's the
14 only way it can happen.

15 So, in fact, *in vivo*, 40 milligrams of
16 doxycycline does, in fact, have a significant inhibitory
17 effect.

18 Now, that Haffajee paper was not before the
19 Court at the preliminary injunction hearing, but we believe
20 that you will find it persuasive and dispositive.

21 Now, Galderma's expert, Dr. Webster, who has
22 been a paid advisor to Galderma for many years, relies on
23 studies as it did with the FDA. And originally, there were
24 three studies that Dr. Webster relied on in his expert
25 report, looking at the trial slides, I am not sure that Dr.

1 Webster will be relying on all three of these reports. He
2 may well be just be relying on the Skidmore report and the
3 Walker 2005 report. That would make sense because the
4 Walker 2000 study actually found under the microscope a
5 significant reduction of bacteria after administration of 40
6 milligrams of doxycycline.

7 Now, none of these studies have what is known as
8 a positive control, which is, it did not have any amount of
9 doxycycline that would have been expected to have an
10 antibiotic effect.

11 So the authors of these studies are unable to
12 say if it would have been any different with an amount over
13 what Galderma claims to be the antibiotic threshold. They
14 just don't have that.

15 There are other problems as well, as Dr.
16 Chambers will discuss.

17 These are by no means at all dispositive on the
18 question of sub-antibacterial formulation. In fact, they
19 are weak and limited.

20 Now, there has been a discussion, certainly, of
21 Mr. Flattmann offered this morning, that Mylan's proposed
22 label renders its infringement claims invalid. But that is
23 actually not supported by the label. We will show the Court
24 that.

25 If you look at the label there are two sentences

1 that Galderma has pointed to. The first is that the plasma
2 administration -- the plasma concentrations of doxycycline
3 are achieved with Oracea during administration are less than
4 the concentration used to treat bacterial diseases.

5 That is true. We don't dispute it.

6 However, the question here is whether, if you
7 have an amount that would not be useful for the treatment of
8 bacterial diseases does it therefore not inhibit bacteria.
9 And I don't believe you will find any evidence establishing
10 that as a fact. In fact, it's not the truth.

11 Doctors prescribe a sufficient amount of an
12 antibiotic to do the job. They don't try to undershoot.
13 They try to overshoot. They want to get the job done.

14 The other sentence that apparently is relied
15 upon, In vivo microbiological studies utilizing a similar
16 drug exposure for up to 18 months demonstrated no detectable
17 long-term effects on bacterial flora of the oral cavity,
18 skin, intestinal tract, and vagina.

19 We don't dispute that. But that does not
20 eliminate the possibility of significant effects in
21 bacterial flora in other parts of the body, nor does it
22 affect the question or even address the question as to
23 whether there are interim effects with respect to bacterial
24 concentrations in the body, and the difference is
25 significant.

1 The Court in its injunction memorandum cited to
2 Bayer v. Elan. That case says that, quote, An ANDA
3 specification defining a proposed generic drug in a manner
4 that directly addresses the issue of infringement will
5 control the infringement inquiry.

6 Your Honor, that holding was based on the
7 observation that the FDA approves labels and a generic
8 manufacturer would not risk selling a product that differed
9 from the specification in the label.

10 In the case in *Bayer*, the specification question
11 was natural and numerical value. The language used the
12 Mylan's label does not directly address the question as to
13 whether 40 milligrams of doxycycline will not significantly
14 inhibit the growth of microorganisms. However, an
15 examination of the label is in fact quite usable and
16 unfavorable to the plaintiffs, because the evidence will
17 show that CollaGenex repeatedly attempted to solve the label
18 for Oracea with favorable patent language but the FDA would
19 not allow it.

20 These are just some of the statements that were
21 rejected by the FDA. The first one is, the plasma
22 concentration of doxycycline achieved with this product
23 during administration is well below the level required to
24 inhibit microorganisms commonly associated with bacterial
25 diseases.

1 That would have been read on the patent. It was
2 rejected by the FDA.

3 CollaGenex also asked for the dose and formulas
4 of doxycycline monohydrate demonstrates no effect on
5 bacteria sampled from the oral cavity, skin, feces and
6 vagina. Does not result in development of or increased
7 resistance to the tetracycline or other classes of
8 antibiotics among common bacteria found in various anatomic
9 cites.

10 The FDA also rejected that.

11 Third, and there are more, but third is while
12 Oracea has been demonstrated to have no antimicrobial
13 activity, it has been shown in vitro to suppress no
14 inflammatory processes such as neutrophil activation,
15 inhibition of matrix metal proteases, endogenous nitric
16 oxide release, and expression of inducible nitrous oxide
17 synthase.

18 And you see, in this attempted language, they
19 tried to solve the language of the Ashley patents and the
20 Amin patents. The FDA rejected it.

21 Your Honor, just as CollaGenex or Galderma
22 couldn't prove to the FDA that Oracea will not significantly
23 inhibit the growth of microorganisms, the evidence will be
24 better here on a full trial of all the evidence.

25 The burden of proof is critical on the Court's

1 ruling on this issue because none of the claims of the
2 Ashley patent are limited to a subset of microorganisms or
3 to a specific body or location or to specific time period.
4 Ashley, therefore, contains a negative limitation applicable
5 all microorganisms at all places in the body.

6 Because plaintiffs' evidence will not show that
7 there is no significant inhibition of growth with respect to
8 all microorganisms, anywhere in the body, they will not meet
9 their burden.

10 Let me introduce our Ashley experts to the
11 Court. They're all in the courtroom. And perhaps they
12 could stand when I will mention them.

13 Dr. Randall Stafford from Stanford School of
14 Medicine. Dr. Stafford will testify corroboratively to
15 Dr. Feldman. Dr. Stafford is an expert in epidemiology. He
16 studies the prescription data and will show Dr. Feldman had
17 a description filter of Periostat, so did many other
18 dermatologists, before the Ashley patent.

19 Dr. Barbara Gilchrest is the Emeritus Chair of
20 the Department of Dermatology at Boston University. She
21 will testify as to invalidity.

22 And Dr. Henry Chambers.

23 Thank you, doctor.

24 Dr. Chambers will testify on infringement. He
25 is the Professor of Medicine, the division of infectious

1 diseases. His is an expert on antibiotics and antibiotic
2 effect.

3 Let me turn now to the Amin patents.

4 The Amin patents were not used at the
5 preliminary injunction hearing. I think there is a good
6 reason they weren't. They are very weak and they don't
7 apply to the Mylan product.

8 There is a summary of our arguments on Amin.

9 There is no evidence that 40 milligrams of
10 doxycycline administered daily decreases endogenous nitric
11 oxide production or inhibits iNOS expression, which is what
12 the patent is about.

13 We don't dispute that doxycycline at a much,
14 much higher dose will have that effect. Our product doesn't
15 have the much, much higher dose. It only has a 40 milligram
16 dose.

17 And so what we see that the plaintiffs tried to
18 do with respect to this particular patent is they rely on a
19 syllogism and the syllogism is that although there is no
20 direct evidence that 40 milligrams of doxycycline will
21 inhibit either nitric oxide or iNOS, it treats rosacea.
22 Therefore, they say since rosacea is a disease that is
23 caused by these processes and since you are carrying the
24 disease, they will argue you must be addressing this
25 underlying cause of nitric oxide and iNOS expression.

1 The problem with this, of course, is that there
2 is no proof of this either. The experts who advances the
3 theory of infringement relied on articles, reviewed the
4 actual studies. As we will show, the actual studies looked
5 at the underlying research and, in fact, rejects the notion
6 that rosacea is caused by nitric oxide or inducible nitro
7 oxide synthase or that reducing nitric oxide or inducible
8 nitro oxide synthase causes a reduction in acne rosacea.

9 In fact, now and in the past, the exact etiology
10 of acne rosacea is unknown except that no one has come to
11 the conclusion in the published articles that relied upon by
12 experts to say that this rosacea is in fact a product of
13 these nitric oxide functions.

14 Mylan's expert Dr. Robbins will explain how
15 these articles have been misconstrued and will explain how
16 rosacea is a multibacterial disease. The literature does
17 not support a conclusion that nitro oxide production by
18 inducible nitric oxide synthase is a factor in the
19 pathogenesis of rosacea.

20 Dr. Robbins will also explain how the data that
21 is available regarding the effect of administering
22 40 milligrams of doxycycline supports the conclusion that
23 Mylan's generic version of Oracea will not decrease
24 endogenous nitric oxide production and will not inhibit iNOS
25 expression.

1 It turns out that the very arguments Galderma
2 uses to try and show infringement, which is the syllogism.
3 You treat the disease. The disease is caused by the nitric
4 oxide issues, therefore you are practicing the invention, if
5 accepted, would actual invalidate the Amin patents.

6 The reason for that Galderma claims the
7 administration of Oracea inhibits nitric oxide and iNOS
8 expression. Galderma claims this happens because the
9 administration of 40 milligrams of doxycycline giving once
10 per day creates a steady state blood serum concentration
11 that decreases and inhibits these chemicals.

12 However, if just the administration of 40
13 milligrams of doxycycline practices the invention, this
14 means that the many, many articles describing the use of
15 20 milligrams of doxycycline twice daily treat inflammatory
16 disease such as arthritis, rheumatoid arthritis and
17 periodontitis inherently anticipate the claims of the Amin
18 patents.

19 In other words, the link that Galderma claims
20 exists between its medicine and the decrease in nitric oxide
21 and inhibition of iNOS expression, if it really does exist,
22 then it has existed all along. It's an inherent property of
23 doxycycline, and the prior art would invalidate the Amin
24 patents.

25 Our expert on the Amin patents is Dr. Richard

1 Robbins.

2 Dr. Robbins. Thank you.

3 Dr. Robbins is a practicing physician. He is
4 also a former Professor of Medicine at LSU. He has done
5 extensive and recognized research in the fields of nitric
6 oxide and its effect on the body.

7 Let's talk about the Chang patent. The Chang
8 patent issued during the pendency of Galderma's lawsuit. We
9 will not dispute infringement except as to claims 4 and 18.
10 However, we strongly contest the validity of all the
11 asserted claims and will show by clear and convincing
12 evidence that the Chang patent is entirely invalid. It
13 should never have been issued.

14 Here is a summary of the ways that it is
15 invalid. We will show invalidity three ways:

16 First, the patent was anticipated.

17 Second, the patent was obvious. The formulation
18 was obvious. And,

19 Third, the critical limitation of the patent was
20 not invented by the named patent inventors. It was invented
21 by an unlisted inventor, communicated to the named
22 inventors, thus rendering the patent invalid under Section
23 102(f).

24 Now, Chang describes a formulation of 40
25 milligrams of doxycycline that consists of beadlets in an

1 approximate 3 to 1 ratio. 3 to 1. Instant release versus
2 delayed release. Formulation is administered once a day to
3 achieve drug levels in blood serums at steady state between
4 .1 and 1.0 micrograms doxycycline per milliliter.

5 Your Honor, the evidence will show that this is
6 a simple, pedestrian formulation exercise, entirely
7 predictable and one was that was designed to extend the
8 lifetime of Galderma's Periostat drug franchise.

9 Your Honor, the evidence will show this is just
10 drug ever-greening at its worst, a nontherapeutic
11 modification of an existing drug performed solely to avoid
12 competition, and that is exactly how it was conceived.

13 This is the May 2001 internal CollaGenex memo
14 why they are doing once-a-day Periostat development. Though
15 they have this twofold, but number one is, of course, to
16 develop a proprietary once-a-day Periostat formulation that
17 could be patented worldwide, protecting the Periostat
18 franchise.

19 They weren't trying to solve any problems or fix
20 the world, they were just trying to extend the franchise to
21 keep people out of the 40-milligram doxycycline market.

22 Now, this was developed by a company called
23 Shire Labs. Mr. Flattmann said it was Supernus. Supernus
24 acquired the assets of Shire Labs. At the time, the company
25 was called Shire so we have succession issues. We have

1 Shire and Supernus with CollaGenex and then today Galderma,
2 so sometimes those names, they're not interchangeable but
3 they're the same parties.

4 Now, Shire signed a contract with CollaGenex and
5 they took known technology from instant release and extended
6 release beadlets in an entirely predictable manner to create
7 the invention. CollaGenex selected the formulation designs
8 essentially from a catalog, and here in essence is the
9 catalog.

10 This is the Shire memo. And what they do is
11 discuss how they're going to do Periostat XR, what they call
12 once-a-day Periostat. What they say is we use their
13 Microtrol technology, and that is what they use. They
14 already had the technology on the shelf and that is what
15 they used.

16 Your Honor, it was entirely predictable because
17 every element of the Chang patent is based on long
18 understood and known properties of doxycycline. The Chang
19 patent was fully anticipated by Galderma's Mr. Ashley and
20 previously filed patent applications, not surprisingly since
21 Mr. Ashley directed this development and indeed Mr. Ashley
22 claims in his patent application to have invented the
23 combination formulation of doxycycline found in the Chang
24 patent, not the exact numbers but the formulation strategy
25 and method. The Chang patent is not just invalid for

1 anticipation but it's invalid as obvious and indeed
2 painfully so.

3 Dr. Rudnic, the former Shire executive who now
4 returns as an expert to vouch for Shire's invention, in his
5 prior testimony posited two elements of novelty to the
6 invention. One, it allows once-daily oral dosing. And,
7 two, it reflects learning on how doxycycline is absorbed in
8 the body.

9 But far from novel, these two elements are
10 known to any person skilled in the art regarding the
11 pharmacokinetics of doxycycline. First, the single daily
12 dose is not only known in the art, it's on the label. This
13 is Vibramycin again. They're talking about a maintenance
14 dose administered as a single dose, RX 50 milligrams every
15 12 hours.

16 So doxycycline has been known really since
17 the dawn of the drug it is susceptible to a single dose
18 because of its half-life. It's a straight function of its
19 half-life.

20 And to quote Mr. Ashley:

21 "Question: Were you the person who came up with
22 the idea that it would be useful to have a once-daily
23 formulation of doxy?"

24 "Answer: I believe so. However, that step, for
25 want of a better word, is not particularly interesting.

1 It's obvious, in and of itself."

2 And we agree with Mr. Ashley.

3 As to the absorption profile of doxycycline,
4 that is that it's absorbed in the upper small intestine, the
5 duodenum, that too had been understood forever. And, again,
6 this is Mr. Ashley commenting on it.

7 "Question: Okay. And point number 4 here is
8 quote, 'it is believed that doxy is only absorbed in the
9 upper GI tract and released lower in the colonic region is
10 not desired.' And that is consistent with what you told me
11 earlier; is that correct?

12 "Is that correct?

13 "Answer: The literature suggested that at the
14 time, yes."

15 So this is nothing new here in the Chang patent.
16 It's based on concepts that are admitted to be well known.

17 And last, but by no means least, on the question
18 of the Chang patents invalidity, the evidence will show that
19 serious contradiction that the key element of the Chang
20 claims, the 3 to 1 ratio, was not invented by the Chang or
21 his fellow named inventors. Indeed, but for this 3 to 1
22 ratio, there is little or no difference between Chang --
23 between the Chang and Ashley patents which claimed sustained
24 release preparation. If there is any secret sauce, this is
25 the secret sauce.

1 But Chang and his colleagues at Shire did not
2 invent this ratio. Indeed, Dr. Chang was quite clear on
3 this. The named inventor.

4 "Question: Okay. Among the three of you --
5 there are three named inventors on the patent, your Honor --
6 who was the person who first came up with the concept of
7 such a formulation having a 3 to 1 ratio of IR to DR
8 portions?

9 "Answer: The ratio I think is picked by the --
10 the CollaGenex, but based on our data, all simulation data
11 sent to -- to -- to CollaGenex and after discussion they --
12 they picked the ratio."

13 There is no question that before CollaGenex
14 picked the ratio, the inventors hadn't even simulated a 3 to
15 1 ratio. In other words, the investor was CollaGenex here.
16 The inventor is not listed and, under the patent law, that
17 makes it invalid.

18 Now, really remarkably, when there is an
19 inventorship issue, there is no inventor here to defend the
20 patent. None of the three inventors are going to come to
21 Court and say that they invented this patent. In fact, none
22 of the inventors are coming into court to defend any of the
23 patents. The only defenders of the patents are the experts
24 hired by Galderma, and of them, they had previously
25 relationships with the parties involved.

1 Now, I should say, again, I have not given you
2 all of the evidence that we're going to present obviously,
3 so I hope the Court will not believe that we're limited by
4 everything in here. The invalidity actually goes beyond the
5 Ashley patents, but for time and to move on to evidence, I
6 haven't covered every piece of testimony that we plan to
7 present.

8 I want to talk briefly about the secondary
9 considerations of obviousness. And the first question is
10 was there a long felt need for this 3010 Pallidin counsel?
11 Was there something that 50 milligrams really didn't satisfy
12 in the market? Well, to the contrary, the evidence will
13 show not only was there no long felt need, there was no need
14 and you don't have to go actually beyond the Chang patent
15 itself to understand that this is from the Chang patent.
16 And Chang says, it was surprisingly found that these
17 levels -- and they're talking about these sub-antibiotic
18 levels -- can be accomplished with a single daily dose of an
19 immediate release formulation containing below 50 milligrams
20 but more than 25 milligrams, preferably about 40 milligrams
21 of doxycycline base. So basically they could have
22 accomplished according to the patent, the same invention by
23 simply taking two Periostats once-a-day instead of taking
24 one twice-a-day.

25 The only long felt need that was served here was

1 need for CollaGenex to create a formulation patent to keep
2 competitors out of the market, and that is all this is.

3 There is no evidence that you will hear that has
4 any advantage over a 50-milligram doxycycline product. And,
5 in fact, I don't believe you will hear any evidence of any
6 comparison between a 40 and a 50-milligram product.

7 While the patent of the Ashley patents do say
8 that 50 milligrams is antibiotic, we stipulated to it. The
9 number was not picked with any precision. We believe
10 50 milligrams is antibiotic. We believe 40 milligrams is
11 antibiotic.

12 Indeed, while Oracea has had great sales and
13 success, it is driven by a very clever and voluminous, very
14 heavy marketing, but the marketing really doesn't have any
15 nexus to the patents before the Court.

16 The core of the Galderma marketing is what is
17 called direct to consumer. In other words, what they're
18 trying to do is most people just live with their rosacea and
19 don't go to the dermatologist. They try to drive consumers
20 to their dermatologist.

21 So, for example -- actually, before I get to
22 that, let me talk about our experts.

23 On invalidity, we have Dr. Werner Rubas.

24 Werner.

25 Dr. Rubas is a recognized expert in the field of

1 pharmacokinetics. And Dr. Rubas will talk about, will
2 explain why the formulation is a simple function of known
3 knowledge about the characteristics of doxycycline.

4 We also have Dr. David Friend -- thank you, Dr.
5 Friend -- who is a recognized leader in product development
6 and formulation. He is currently at the CONRAD program at
7 the Eastern Virginia Medical School, which he will tell the
8 Court about.

9 So let me return to secondary considerations.

10 This is how Oracea has gotten its success, with
11 things such as the emotional impact of rosacea, telling us
12 that rosaceas' physical symptoms can be frustrating enough,
13 but its impact can reach well beneath the surface. Of
14 course, Oracea only touches the surface.

15 It talks being more likely to be insecure in a
16 relationship. And the good news: Another survey from the
17 National Rosacea Society, 88 percent of respondents stated
18 that effective medical therapy improved or somewhat improved
19 their condition.

20 At the bottom, it refers people come to this
21 website, to the helpful dermatologist tool base.

22 So this is the sort of advertising that can be
23 frankly used to advertise 200 milligrams of doxycycline or a
24 face cream. It has nothing to do with any 3 to 1 ratio of
25 IR to DR pellets and it is attributed to a very

1 sophisticated sales program, but it doesn't actually reflect
2 any great innovation or any innovation at all.

3 Speaking on commercial success for Mylan will be
4 Dr. Phil Nelson.

5 Dr. Nelson.

6 Dr. Nelson is principal of Economists,
7 Incorporated and is much experienced in analyzing sales and
8 their source, and we will be presenting his testimony to the
9 Court.

10 Your Honor, there are five patents here but the
11 evidence will show clearly and convincingly that none of
12 them are valid.

13 As to all but one Mylan's ANDA product is not
14 infringed, even if that the patents were valid.

15 These are invalid patents that should not stand
16 to exclude Mylan from competing in this market.

17 Your Honor, we are aware, keenly aware that this
18 Court's first analysis of evidence related to these patents
19 was adverse to Mylan and that we have a burden to convince
20 the Court otherwise. However, we believe that upon
21 presentation of all the evidence at this trial, the Court
22 will agree with Mylan that these patents should not prevent
23 Mylan from selling the generic product pursuant to the
24 Hatch-Waxman Act.

25 We will at the close of evidence ask the Court

1 to dissolve the injunction and enter a judgment in favor of
2 Mylan.

3 Thank you.

4 THE COURT: Okay. Thank you. Let's begin with
5 the first witness.

6 MR. FLATTMANN: Your Honor, Galderma calls Dr.
7 Guy Webster to the stand.

8 ... GUY WEBSTER, having been duly sworn as a
9 witness, was examined and testified as follows ...

10 THE COURT: Good morning, Dr. Webster.

11 MR. FLATTMANN: Your Honor, with the Court's
12 permission, I will hand up some binders of the exhibits that
13 will used during the course of the examination.

14 THE COURT: That is fine. Two copies.

15 MR. FLATTMANN: Yes, Your Honor.

16 DIRECT EXAMINATION

17 BY MR. FLATTMANN:

18 Q. Good morning, Dr. Webster.

19 Could you please state your full name for the
20 record.

21 A. Guy Webster.

22 Q. What do you do for a living?

23 A. I am a dermatologist.

24 Q. What is your job?

25 A. I treat patients with skin disease.

Webster - direct

1 Q. Can you tell us about your clinical practice?

2 A. It's in Hockessin, Delaware, with my wife. I went
3 there about six years ago after leaving Jefferson Medical
4 College. And I see a lot of patients there.

5 Q. What is the size of your clinical practice?

6 A. There are 43,000 charts on the walls.

7 Q. What educational degrees do you hold?

8 A. I have a Bachelor's degree from the University of
9 Pennsylvania. A Ph.D. from Penn in pathology, which was
10 really immunology. And an M.D. from Penn as well.

11 Q. What was the focus of your Ph.D. in pathology?

12 A. It was looking at how bacteria gets the immune system
13 excited, specifically about mechanisms of information in
14 acne.

15 Q. After you finished your M.D. in 1985, what was your
16 next academic appointment?

17 A. I was an intern at the University of Pennsylvania and
18 then I went to New York University as a dermatologist.

19 Q. What was your next academic appointment?

20 A. Assistant professor at Jefferson Medical College.

21 Q. What did you do next?

22 A. Associate professor, then full professor and chief of
23 the clinic at Jefferson and vice chairman.

24 Q. As a professor, what sort of courses and lectures did
25 you give?

Webster - direct

1 A. I taught general dermatology to medical students and
2 then more specific courses to more advanced residents and
3 doctors in that respect.

4 Q. Have you published much in your field?

5 A. Yes, I have.

6 Q. About how many articles and books have you published?

7 A. A couple hundred.

8 Q. Have you published any articles in the field of
9 microbiology?

10 A. About 30.

11 Q. Are you on the editorial boards or a reviewer for any
12 academic journal?

13 A. I am on the editorial board of the Journal for the
14 Academy of Dermatology, and I review for every English
15 language journal that I know of, as well as the New England
16 Journal of Medicine and the British Medical Journal.

17 Q. Are you a member of any professional societies?

18 A. I am a member of the Society for Investigative
19 Dermatology Society, the American Academy of Dermatology,
20 the American Dermatological Association.

21 Q. Have you heard of the American Academy on Acne and
22 Rosacea Society?

23 A. I have. I left that out. I was the founding
24 president. The AARS is a group of doctors who have gotten
25 together to see that acne and rosacea remain diseases that

Webster - direct

1 get scientific focus and remain diseases that insurers are
2 willing to pay for.

3 There is a move to trivialize acne and rosacea
4 and take it out of the medical spectrum and make it a
5 cosmetic disease, which would be a tragedy.

6 Q. Generally, how would you describe your fields of
7 expertise?

8 A. I am an expert in dermatology in general and
9 inflammatory diseases in particular.

10 Q. Dr. Webster --

11 MR. FLATTMANN: May I approach the witness?

12 THE COURT: You may.

13 BY MR. FLATTMANN:

14 Q. I am going to hand you your witness book and also
15 your book of slides.

16 Could you please turn in your Exhibit binder to
17 Plaintiffs' Trial Exhibit 248?

18 What is it?

19 A. It's my curriculum vitae.

20 Q. Does it fairly and accurately summarize your
21 education, employment, scientific work, publications and
22 professional accomplishments?

23 A. It does.

24 BY MR. FLATTMANN: Your Honor, I offer Exhibit
25 PTX-248 into evidence.

Webster - direct

1 MR. STEUER: No objection.

2 THE COURT: It is admitted.

3 (Plaintiffs' Trial Exhibit No. 248 received in
4 evidence.)

5 MR. FLATTMANN: I proffer Dr. Webster as an
6 expert in clinical dermatology and microbiology.

7 THE COURT: Any objection?

8 MR. STEUER: No objection.

9 THE COURT: He is so recognized.

10 BY MR. FLATTMANN:

11 Q. Doctor, please turn in your slide binder to the
12 slides that are marked as Plaintiffs' Demonstrative Exhibits
13 101 through 141. I understand that you will be using slides
14 to assist you in your testimony today. Is that correct?

15 A. Correct.

16 Q. How did you build up preparing these slides?

17 A. I prepared them along with the assistance of counsel.

18 Q. Please turn to the first slide, PDX-101. What have
19 you shown here?

20 A. I have shown here a summary of my opinions,
21 specifically, that Claims 1, 22, 23, 26, 28 and 30 of the
22 Ashley '267 patent are infringed, and Claims 1, 12 to 15,
23 20, 21, 23, 24 and 26 of the '572 patent are infringed.

24 Furthermore, both patents, invalid, not
25 anticipated, and nonobvious and the claimed methods of the

Webster - direct

1 Ashley patients were surprising and met a long-felt need in
2 2000.

3 Q. And I will ask you about the details of those
4 opinions one at a time as we get to each of them. Could you
5 turn to the next slide, please?

6 What have you shown here?

7 A. That is description of rosacea. It is a chronic,
8 meaning long-lasting, inflammatory disorder, mostly of the
9 face. It is a collection of symptoms, not all of them are
10 present at the same time.

11 A common denominator is flushing and blushing or
12 erythema of the face. Many patients get pimple-like bumps
13 which are termed papules and pustules, and there are visible
14 blood vessels and enlarged W.C. Fields looking noses which
15 sometimes occur, which is called rhinophyma.

16 Q. What is the occurrence of rosacea in the United
17 States?

18 A. About 13 or 14 million patients have rosacea.

19 Q. What causes it?

20 A. The cause seems mostly to be related to the
21 deposition of inflammatory protein in the skin. The immune
22 system has a wealth of activity called the innate immune
23 system, which is preformed immunity designed to deal with
24 invading organisms before a true antibody response can be made.

25 One of the peptides in the innate immune system

Webster - direct

1 is designed to kill bacteria. If it is cut in half at the
2 wrong place it becomes an inflammatory molecule instead of a
3 self-defense molecule. And Rich Gallo at UC San Diego
4 issued very clear the patients with inflammatory rosacea
5 have a lot of this peptide deposited in the skin and this
6 peptide is cleaved in a funny way, not usual way. And that
7 seems to be the cause of rosacea.

8 Q. How does the dysregulation of the immune system lead
9 to rosacea, in your view?

10 A. Well, the dysregulation leads to the formation of an
11 inflammatory situation in the cheeks. And pimples and
12 redness develop from them.

13 Q. How long has that been understood?

14 A. Three, four years, something like that.

15 Q. Could you please turn in your witness book to
16 Plaintiffs' Trial Exhibit 426.

17 Do you recognize it?

18 || A. I do.

19 Q. What is it?

A. This the Oracle package insert label.

21 MR. FLATTMANN: Your Honor, I offer Exhibit
22 PTX-426 into evidence.

23 || MR. STEUER: No objection.

THE COURT: It is admitted.

25 (Plaintiffs' Exhibit No. 426 received in

Webster - direct

1 evidence.)

2 BY MR. FLATTMANN:

3 Q. Let's turn to page GAL22993 in PTX-426 if you would,
4 please, and turn to Section 11, Indications and Usage?

5 According to the Oracea label, what is FDA
6 approved indication for rosacea?

7 A. The treatment of only inflammatory lesions, papules
8 and pustules.

9 Q. And what are papules and pustules? What sorts of
10 cells are associated with the papules and pustules of
11 rosacea?

12 A. Neutrophils and lymphocytes.

13 Q. What are neutrophils and lymphocytes?

14 A. They are white blood cells that are involved in the
15 defense of infection.

16 Q. Could you please turn to PTX-368 in your witness
17 book?

18 Do you recognize this document?

19 A. Yes. It is a review of the pathophysiology of
20 rosacea.

21 Q. By whom?

22 A. By McAleer, Lacey and Powell.

23 Q. How if at all does this publication support your view
24 of which cells are associated with the papules and pustules
25 of rosacea?

Webster - direct

1 A. This publication reviews the papers that have
2 discovered the lymphocytes and neutrophils involved in the
3 information on rosacea.

4 MR. FLATTMANN: I offer 368 into evidence, Your
5 Honor.

6 MR. STEUER: No objection.

7 THE COURT: It is admitted.

8 (Plaintiffs' Trial Exhibit No. 368 received in
9 evidence.)

10 BY MR. FLATTMANN:

11 Q. Please turn to Page 665 in PTX-368 if you would,
12 beginning with the sentence In the early stages the
13 superficial perivascular lymphocytic infiltrate appears
14 marked. Could you please explain that statement to us?

15 A. I am still trying to find it.

16 Q. It is in the upper right-hand corner.

17 A. Yes. In the early stages the superficial
18 perivascular lymphocytic infiltrate appears marked, meaning
19 that the lymphocytes come in and early.

20 Q. How does that excerpt relate to your opinion
21 concerning the cells involved with the papules and pustules
22 in rosacea?

23 A. It confirms it.

24 Q. How does it do so?

25 A. It does so by basically quoting the data that I used

Webster - direct

1 to form my own opinion.

2 Q. What role if any do those cells actually play in the
3 pustules and papules of rosacea?

4 A. These blood cells are intimately involved in the
5 papules and pustules. They are why the papules and pustules
6 happen. If you don't have them, you can't form papules and
7 pustules.

8 Q. Historically, how had Oracea been treated prior to
9 the introduction of Oracea?

10 A. It had been treated mostly with higher dose oral
11 antibiotics.

12 Q. Were there any problems with that therapeutic
13 regimen?

14 A. Yes, there were a good deal of problems. Many
15 patients get GI upset, nausea, diarrhea, and cramping from
16 doxycycline. And also doxycycline is a very active
17 phototoxin, meaning that combined with sunlight in high dose
18 you get a heck of a sunburn. It made it very tough to treat
19 rosacea in the summer time.

20 Q. In your experience, how did dermatologists view these
21 safety concerns and side effects in the 1980s and 1990s?

22 A. They viewed them as a big pain in the neck. It was
23 difficult.

24 Q. When were these problems first solved?

25 A. When Oracea came out in a dose that didn't make the

Webster - direct

1 GI side effects too bad and was too low for any reasonable
2 number of people to get sunburn.

3 Q. Let me ask you to turn back to Plaintiff's Trial
4 Exhibit 426 in your witness book, the Oracea label, and look
5 at the Section 11 description, if you would?

6 A. Yes.

7 Q. What dose of doxycycline does Oracea provide?

8 A. 40 milligrams.

9 Q. Does that dose significantly inhibit the growth of
10 microorganisms?

11 A. It does.

12 Q. How do you know that?

13 A. It says so in the microbial section of the files.

14 Q. In terms of efficacy, how does Oracea compare to the
15 earlier higher doses of doxycycline used in the treatment of
16 rosacea?

17 A. It seems to be the same.

18 Q. In terms of safety, how does Oracea compare to the
19 early higher doses of doxycycline in the treatment of
20 rosacea?

21 A. It is vastly superior. There are essentially no GI
22 side effects greater than that seen in plasma and there is
23 no sunburn.

24 Q. How has the introduction of Oracea affected your
25 clinical practice?

Webster - direct

1 A. It has made it a lot easier to treat patients in
2 the summer.

3 Q. Please turn to the next slide in your binder,
4 PDX-103, if you would. What are in vitro antibiotics
5 susceptibility tests?

6 A. In-vitro tests are those done in the laboratory. In
7 this case, it's a test of antibiotics for their ability to
8 inhibit the growth of microorganisms in a very isolated,
9 artificial system.

10 Q. How generally are these tests conducted?

11 A. They are conducted either in a tube with the bacteria
12 growing or not growing in a broth or on an agar plate with
13 the disk of antibiotic that diffuses outward and bacteria
14 grow up to a certain point.

15 Q. You had mentioned minimum inhibitory concentration or
16 MIC on this slide? What is that?

17 A. That is the property of the bacteria that you detect
18 with in-vitro testing. It is the amount of, least amount of
19 bacteria that it will be inhibited by.

20 Q. What is the significance of identifying the MIC in
21 vitro?

22 A. It has been established for resistance and since
23 activity to antibiotics and you want to know if the organism
24 that you culture from a patient with an infection will
25 respond because of its level of resistance.

Webster - direct

1 Q. What does the MIC tell you about the minimum amount
2 of an antibiotic that would be required to inhibit the
3 growth of the microorganisms in a human subject in vivo?

4 A. It doesn't tell you anything. The number is not
5 directly extrapolatable to the clinical situation because
6 there is too many other factors that the laboratory test did
7 not consider.

8 Q. What types of factors?

9 A. Factors like binding the antibiotic to plasma
10 proteins in the blood which inactivates it or bacterial
11 defense structures, for want of a better word, forces called
12 biofilms that they build infectious sections in order to
13 fight both the host response of white blood cells as well as
14 presumably antibiotics.

15 Q. Please turn to Slide 104, if you would, PDX-104.
16 What are in vivo clinical microbiology studies of
17 antibiotics?

18 A. In-vivo studies are those conducted in living
19 organisms. And since we are dealing with people, in people.

20 Q. What types of effects are generally investigated in
21 this in vivo clinical microbiological studies?

22 A. You look to see whether the bacterial flora changes.
23 The bacterial flora are the bacteria that normally belong in
24 and on you. It's a complex mixture, usually, and there is
25 some pretty fascinating microbiology that goes on with the

Webster - direct

1 skin, in the bowel and the mouth. Just like if you are
2 looking at swamp ecology, there are not alligators and
3 mosquitoes and also things that come in transiently and
4 leave. It is a challenge when you are doing microbiology
5 studies in vivo to determine what is a transient and what is
6 not. It's a fascinating subspecialty of microbiology.

7 Q. Well, what if anything can in vivo clinical
8 microbiology studies tell you about whether a given dose of
9 antibiotic inhibits the growth of a microorganism in a human
10 subject?

11 A. That is how you test to see whether a given dose
12 inhibits. You put it into a person and look for an effect
13 on their bacteria.

14 Q. Please turn in your witness book to Plaintiffs' Trial
15 Exhibits 1 and 2, do you recognize these documents?

16 A. Yes.

17 Q. What are they?

18 A. They are the Ashley patents.

19 Q. If I refer to the '267 patents and the '572 patents
20 together as the Ashley patents, will that be okay?

21 A. Yes.

22 Q. Did you review them in forming your opinions in this
23 case?

24 A. I did.

25 Q. What is your general understanding of what the claims

Webster - direct

1 at the end of the two patents pertain to?

2 A. They pertain to the treatment of acne and rosacea
3 with subinhibitory doses of doxycycline.

4 MR. FLATTMANN: Your Honor, I offer Plaintiffs'
5 Trial Exhibits 1 and 2 into evidence.

6 THE COURT: They're admitted.

7 (PTX Nos. 1 and 2 received into evidence.)

8 BY MR. FLATTMANN:

9 Q. Please turn to the next slide binder, Plaintiffs'
10 Deposition Exhibit 105.

11 What are you showing here?

12 A. What I consider someone as a person of ordinary skill
13 in the art at the time of the invention.

14 Q. What did you conclude as to who that person would be?

15 A. It would be someone with an degree and several years
16 of experience with relating to dermatology. That includes a
17 medical doctor with experience in treating patients,
18 diagnosed with acne and rosacea or research in those areas.

19 Q. How did you reach that opinion?

20 A. By thinking about what seems to be reasonable,
21 someone of ordinary skill might be.

22 Q. Now, earlier you stated that in your opinion, Mylan's
23 product infringes certain claims of the Ashley patents.

24 What did you base that opinion?

25 A. I based it on both the claims of the patents and the

Webster - direct

1 stuff in the package inserts.

2 Q. Whose package inserts?

3 A. Mylan's package inserts.

4 Q. Please turn to Defendant's Trial Exhibit 2091.

5 Do you recognize this document?

6 A. I do.

7 Q. What is it?

8 A. This is the Mylan package insert.

9 Q. Did you consider this Mylan package insert in forming
10 your opinions in this case?

11 A. I did.

12 Q. Okay.

13 MR. FLATTMANN: Your Honor, I offer Defendant's
14 Trial Exhibit 2091 into evidence.

15 MR. STEUER: No objection.

16 THE COURT: It's admitted.

17 (DTX No. 2091 received into evidence.)

18 BY MR. FLATTMANN:

19 Q. Please turn to the next slide in your binder PDX-106,
20 please.

21 What have you shown here for us?

22 A. This is the patent claim 1 language in both patents.

23 Q. What is your opinion regarding whether Mylan's
24 product infringes these two claims, claim 1 of each patent?

25 A. It does infringe claim 1 of each patent.

Webster - direct

1 Q. And how did you reach that conclusion?

2 A. By considering the package labeling of Mylan product
3 in claim 1 of both patents.

4 Q. Okay. Please turn to the next slide in the witness
5 book, PDX-107.

6 What are you illustrating here?

7 A. This is a break down of the individual claim elements
8 in '267 and '572, and how it compares with the wording in
9 Mylan's label.

10 Q. Why don't we go through each of those elements.
11 Start on the top row, and we'll highlight these as we go
12 through them for convenience sake.

13 What is your opinion regarding whether Mylan's
14 product meets the element, a method of treating acne in a
15 human in need thereof in claim 1 of the '267 patent?

16 A. In the label it says, indicated for papules and
17 pustules of rosacea which is highlighted in Section 1.1.

18 Q. And what did you conclude from that?

19 A. That's infringing.

20 Q. What is your opinion regarding whether Mylan's
21 product meets the element, a method for treating papules or
22 pustules of rosacea in a human in need thereof in claims 1
23 and 20 of the patent?

24 A. Mylan's label in Section 1.1 says its indicated for
25 papules and pustules of rosacea so it infringes.

Webster - direct

1 Q. Okay. Going to the next row. What is your opinion
2 regarding whether Mylan's product meets the element,
3 administering orally in claim 1 of the '267 and '572
4 patents?

5 A. It's indicated for oral administration, as it says in
6 Section 2, so it infringes.

7 Q. And going to the next row. What is your opinion
8 regarding whether Mylan's product meets the element,
9 antibiotic tetracycline compound in claim 1 of both patents?

10 A. The indication usage says that it's doxycycline and
11 in the label it says the active ingredient is doxycycline.
12 So it infringes.

13 Q. I'm actually having a little trouble hearing you.
14 Could you get closer? I think it would help me the Court
15 and the court reporter.

16 A. Okay.

17 Q. Thanks so much. That's much better. My hearing is
18 bad but I noticed it was a little bit low.

19 A. It's cramped in here.

20 Q. I'm sorry. What is your opinion regarding whether
21 Mylan's product meets the element, amount that reduces
22 lesion count in claim 1 of the '267 patent and the element,
23 amount that is effective to treat the papules and pustules
24 of rosacea in claims 1 and 20 of the '572 patent?

25 A. Mylan's label says it's indicated for papules and

Webster - direct

1 pustules of rosacea and the clinical studies demonstrate a
2 reduction of lesion count, so that infringes. The same
3 wording applies to the second item so that also infringes.

4 Q. Okay. And which clinical studies are you referring
5 to?

6 A. The one cited in Mylan's package inserts.

7 Q. Where are those in the package inserts?

8 A. They're in the microbiology section.

9 Q. What is your opinion regarding whether Mylan's said
10 amount being 10 to 80 percent of the antibacterial effective
11 amount in claim 1 of the '267 patent and the element, said
12 amount being 10 to 80 percent of the antibiotic amount in
13 claims 1 and 20 of the '572 patent?

14 A. The amounts 40 milligrams of doxycycline, which is
15 40 percent of 100 milligrams, and 20 percent of 200
16 milligrams so it infringes.

17 Q. Where do you find that in Mylan's label?

18 A. In the dosage administration section.

19 Q. Okay. Going to the next row, what is your opinion
20 regarding whether Mylan's product meets the element,
21 administered long term in claim 1 of the '267 patent?

22 A. Mylan's label talks about a 16-week clinical efficacy
23 study and it is clearly long term so there is infringement.

24 Q. What is your opinion regarding whether Mylan's
25 product meets the element, without administering a

Webster - direct

1 bisphosphonate compound in the '267 and '572 patent?

2 A. The label makes no mention of bisphosphonate so that
3 would be infringement as well.

4 Q. Let's turn the next slide in your binder, if you
5 would. It's PDX-108.

6 What have you shown here?

7 A. The Ashley patent claims that relate to a
8 subantibacterial amount.

9 Q. What have you highlighted in particular?

10 A. The phrasing in claim 1 of the '267 that is a
11 subantibacterial amount, and the phrasing in '572, an amount
12 that is effective to treat the papules and pustules of
13 rosacea but has substantially no antibiotic activity.

14 Q. In your opinion, does Mylan's product meet these
15 elements?

16 A. Yes, it does.

17 Q. Please turn to the next slide, PDX-109, in your
18 binder. What you have illustrated here?

19 A. The claim terms and the Court's construction.

20 Q. Okay. And how did the Court define these terms?

21 A. They defined it as an amount that does not
22 significantly inhibit the growth of microorganisms.

23 Q. Okay. Did you adopt the Court's definition in
24 forming your opinions in this case?

25 A. I did.

Webster - direct

1 Q. In your opinion, would the use of Mylan's product in
2 accordance with Mylan's label meet the element of,
3 administering a subantibacterial amount?

4 A. Yes, it would.

5 Q. How did you reach that opinion?

6 A. By considering the information in the label and as
7 well as the claims in the Court's construction.

8 Q. Did you reach the same opinion with regard to whether
9 Mylan's, use of Mylan's product in accordance with Mylan's
10 label would meet the element of the '572 patent claim,
11 namely, administering an amount that has substantially no
12 antibiotic activity?

13 A. Yes, it would.

14 Q. It would?

15 A. Yes.

16 Q. And how did you reach that opinion?

17 A. By reading the labels and considering the claims.

18 Q. Okay. Now, specifically what section of Mylan label
19 did you rely on for that opinion?

20 A. The microbiology section.

21 Q. Let's look at the label again, DTX-2091.

22 Can you point out for us where the microbiology
23 section appears?

24 A. It's in Section 12.4.

25 Q. Okay. Let's take a closer look. And we have some

Webster - direct

1 slides on this. Could we look at slide PDX-110, please?

2 What have you highlighted here in the

3 microbiology section of Mylan's section?

4 A. Where it says in vivo microbiology studies using a
5 similar drug exposure demonstrated no detectable long term
6 effects on bacterial flora of the oral cavity, skin,
7 intestinal tract, and vagina.

8 Q. What does this say in telling you whether Mylan's
9 product will be administered in a subantibacterial amount?

10 A. It says several studies looking at the areas of
11 highest bacterial population in the body have shown there is
12 no effect.

13 Q. And therefore?

14 A. And therefore, it's a subantibacterial amount and it
15 infringes.

16 Q. Please turn to Plaintiffs' Demonstrative Exhibit 111.

17 What are you shown here?

18 A. This is the wording of the '572 patent, where it
19 says, the drug will be administered in an amount that
20 results in no reduction of skin microflora during a
21 six-month treatment.

22 Q. What claim of the patent is this from?

23 A. It's claim 1 of the '572.

24 Q. First of all, what is skin microflora?

25 A. Skin microflora are the bacteria that live on the

Webster - direct

1 skin. They are residents and they are transients. The
2 residents are really remarkably stable in their composition
3 and proportion unless the system is perturbed. And
4 perturbation could be something as simple as changing from
5 winter to summer where there is more water present on the
6 skin or occluding the skin by putting a shoe over the foot.
7 The added moisture changes the flora.

8 Q. And going back to this highlighted element in the
9 '572 patent, claim 1, in your opinion, would the use of
10 Mylan's product in accordance with its label meet this
11 element?

12 A. Yes, it would.

13 Q. What is the basis for your opinion?

14 A. The material presented in the label and the claims in
15 the patents.

16 Q. Please turn to slide 112, PDX-112 in your book.

17 Okay. In your opinion, what does the
18 highlighted statement tell you about whether Mylan's product
19 will be administered in an amount that results in no
20 reduction of skin microflora during a six-month period?

21 A. Their package insert wording says clearly that for
22 long term administration, there was no effect on the
23 bacterial flora of the oral cavity, skin, intestinal tract
24 and vagina.

25 Q. What did you conclude from that?

Webster - direct

1 A. That there is no substantial antimicrobial effect.

2 It infringes.

3 Q. Okay. Now please turn to the next slide in your
4 binder. Plaintiffs' Demonstrative Exhibit 113.

5 What have you highlighted here in the
6 microbiology section of Mylan's label?

7 A. This is wording that the FDA approved that says
8 doxycycline should not be used for treating bacterial
9 infections, providing antibacterial prophylaxis or reducing
10 the numbers or eliminating microorganisms associated with
11 any bacterial disease.

12 They said three ways quite clearly to make it
13 clear that this should not be used as an antibiotic.

14 Q. What does this tell you about whether Mylan's product
15 is to be administered in a subantibacterial amount?

16 A. It is being administered in a subantibacterial
17 amount.

18 Q. How did you reach that conclusion?

19 A. By reading the wording in the package insert.

20 Q. Please turn to the next demonstrative in your book,
21 which is PDX-114.

22 What have you highlighted here in Mylan's label?

23 A. Wording from the label where it says, the plasma
24 concentration of doxycycline achieved with doxycycline
25 during administration are less than the concentration

Webster - direct

1 required to treat bacterial diseases.

2 Q. What does that statement tell you about whether
3 Mylan's product will be administered in a subantibacterial
4 amount?

5 A. It will be administered in a subantibacterial amount.

6 Q. How do you know that?

7 A. It says so.

8 Q. Now, earlier you stated in reaching your conclusion
9 that Mylan's product will be administered in
10 subantibacterial amount. You also relied on clinical
11 evidence. What clinical evidence were you referring to?

12 A. The evidence is the microbiology section where they
13 studied the effects on normal flora of the skin and other
14 organs and showed there was no effect.

15 Q. Okay. Why did you rely on those studies?

16 A. They were in the label. They came from reputable
17 journals. The FDA approved them. They are trustworthy.

18 Q. Now, let's talk about some of those in vivo studies.
19 If you could turn in your witness book to PTX-394, please.

20 Do you recognize it?

21 A. I do. This is the Skidmore paper.

22 Q. What is the Skidmore paper?

23 A. It's studying the effects of the subantimicrobial
24 dose doxycycline in the treatment of moderate acne.

25 MR. FLATTMANN: Your Honor, I offer PTX-394 into

Webster - direct

1 evidence.

2 MR. STEUER: No objection.

3 THE COURT: It's admitted.

4 (PTX No. 394 received into evidence.)

5 BY MR. FLATTMANN:

6 Q. Please turn to the next slide in your binder,

7 PDX-115.

8 What was the design of the Skidmore study?

9 A. It was a six-month randomized double blind placebo
10 controlled studies in patients with moderate facial acne.
11 They got either 20 milligrams twice daily doxycycline or
12 placebo; and besides having the acne study, they had their
13 skin microflora samples collected at the start and the end
14 of the study.

15 Q. Please turn to the next slide in your book, PDX-116.

16 What were the results of the Skidmore study?

17 A. These are the results that talk about the change in
18 skin microflora. After the entire length of the study, they
19 showed there were no changes both in specific microorganisms
20 and in very large groups such as all anaerobes and all
21 aerobes. There were no changes before and after.

22 Q. What did those results tell you about whether a
23 20-milligram twice daily dose of doxycycline is a
24 subantibacterial amount?

25 A. It is a subantibacterial.

Webster - direct

1 Q. How do you know that?

2 A. There is no effect on the bacteria. So after a long,
3 long exposure, no events emerged.

4 Q. Well, what do these results tell you about whether
5 the once daily dose of Oracea or Mylan's proposed product
6 constitute a subantibacterial of doxycycline?

7 A. They do constitute a subantibacterial amount. It's a
8 similar drug exposure.

9 Q. How do you know it's a similar drug exposure?

10 A. It says so on the label.

11 Q. Now, please turn to the next slide in your binder,
12 PDX-117. What have you shown here?

13 A. The wording from the microbiology section showing the
14 in vivo microbiological studies using a similar drug
15 exposure for up to 18 months demonstrated no detectable long
16 term effects on the flora, oral cavity, intestinal tract,
17 skin and vagina.

18 Q. Which portion of the label is this?

19 A. The microbiology section.

20 Q. How, if at all, does the Skidmore study support your
21 opinion that Mylan's product meets the element, amount that
22 results in no reduction of skin microflora over a six-month
23 period?

24 A. It demonstrates that.

25 Q. How does it demonstrate that?

Webster - direct

1 A. By putting the drug in people for six months and
2 looking for changes.

3 Q. Okay. Please turn to the next slide in your binder
4 PDX-118.

5 What have you shown here?

6 A. This is example 38 from the Ashley patents.

7 Q. What is the relationship between the study described
8 in example 38 and the Skidmore study that we just looked, at
9 Plaintiffs' Trial Exhibit 394?

10 A. This is the same data.

11 Q. Okay. Please turn in your witness book to PTX-413.

12 Do you recognize it?

13 A. I do.

14 Q. What is it?

15 A. It is the Walker paper, long term treatment with
16 sub-antimicrobial dose doxycycline.

17 Q. And what year was the published?

18 A. In 2005.

19 MR. FLATTMANN: Your Honor, I offer PTX-413 into
20 evidence.

21 MR. STEUER: No objection.

22 THE COURT: It's admitted.

23 (PTX No. 413 received into evidence.)

24 BY MR. FLATTMANN:

25 Q. Please turn to the next slide in your binder PDX-119.

Webster - direct

1 What was the design of the Walker 2005 study?

2 A. It was randomized double blind placebo controlled
3 study inpatients with adult periodontitis. They got either
4 20 milligrams twice daily doxycycline or placebo and at
5 baseline three months and six months they had their
6 intestinal and vaginal microflora collected.

7 Q. Please turn to PDX-120.

8 What were the results of the Walker 2005 study?

9 A. They showed that there is no significant inhibition
10 basically. No differences in counts at three months or nine
11 months in fecal and vaginal flora. No significantly
12 significant differences in the proportion, identity of the
13 fecal flora resistance 40 micrograms doxycycline, and no
14 indication doxycycline tended to promote cross or
15 multi-antibiotic resistance.

16 Q. What did those results tell you whether Mylan's
17 generic version of Oracea will constitute a subantibacterial
18 amount of doxycycline?

19 A. It will be a subantibacterial amount of doxycycline.

20 Q. How do you know that?

21 A. Because it has the same -- it shares the same
22 concentration with Oracea, and it's a similar exposure.

23 Q. To what degree does Mylan rely on the Walker 2005
24 study in its proposed label?

25 A. It is in its label.

Webster - direct

1 Q. I'm sorry?

2 A. It's in the label and they rely on it.

3 Q. Okay. Now, we have been talking about in vivo
4 clinical studies of doxycycline in human patients. I would
5 like to ask you about in vitro studies as well. In forming
6 your opinion that Mylan's product will be administered in a
7 subantibacterial amount, did you review the in vitro studies
8 of the antibiotic activity of doxycycline that were studied
9 by Mylan experts?

10 A. I did.

11 Q. What effect did the in vitro data by Dr. Chambers
12 have on your opinion that Mylan's product is administered in
13 a subantibacterial amount?

14 A. It was not persuasive. It was looking at in vitro
15 data being extrapolated to an in vivo setting and you just
16 don't do that.

17 Q. Do you have an understanding of how Dr. Chambers
18 attempted to use the in vitro data to reach conclusions
19 about the in vivo effects of doxycycline?

20 A. Dr. Chambers would have us believe that the
21 concentration that works in vitro is identical to the one
22 that works in vivo, and we know that is not the case.

23 Q. How do you know that is not the case?

24 A. There are many factors involved in antibiotic
25 administration and absorption. People, there is protein

Webster - direct

1 binding and biofilms, as we talked about, and penetration
2 into different compartments of the body, differing for
3 different molecules.

4 Q. Let me ask you to turn to PDX-121 in your book.

5 What have you shown on this slide?

6 A. Some of those variabilities in extrapolating in vitro
7 numbers to in vivo. Biofilms are self-defense structures
8 that impede the penetration of an antibiotic as well as
9 other host mechanisms. Bacteria, they're present in the
10 human organism when there is an infection or flora but
11 they're present in the in vitro test system, so their effect
12 is not taken into account.

13 Tissue penetration, the ability of a drug to get
14 into tissue as needed varies with blood flow to the tissue
15 with the amount of tissue in the tissue as opposed to the
16 amount that is pure water and also whether or not the tissue
17 is lipophilic or Aquaphilic. Certain drugs do well in lipid
18 fat rich tissues and others do better in hydrophilic
19 tissues.

20 And then, finally, a real obvious and easy one
21 is the binding to plasma proteins. We know that antibiotic
22 binding plasma proteins are present in the blood but are
23 inactive and doxycycline in particular bind 90 percent to
24 plasma proteins, so 90 percent of what you use somebody by
25 mouth just plasma proteins alone is inactive in treating

Webster - direct

1 infection.

2 Q. You mentioned that doxycycline is at least 90 percent
3 bound to plasma proteins in vivo. How do you know that?

4 A. It's published, and it's in the label.

5 Q. It's in what label?

6 A. It's in Mylan's label and Oracea's label.

7 Q. Please turn in your book to PTX-362, if you would.

8 Do you recognize this article?

9 A. I do.

10 Q. What is it?

11 A. It's an article by Dr. Chambers and his colleagues
12 looking at the effect of protein binding on daptomycin MIC
13 and antibacterial activity.

14 MR. FLATTMANN: Your Honor, I offer PTX-362 into
15 evidence.

16 MR. STEUER: No objection.

17 THE COURT: It's admitted.

18 (PTX No. 362 received into evidence.)

19 BY MR. FLATTMANN:

20 Q. Please turn to PDX-122.

21 What have you illustrated here?

22 A. Dr. Chambers findings regarding the impact of binding
23 by plasma proteins on the antibiotic activity of a drug
24 called daptomycin. He found that serum MIC for daptomycin
25 was 20 times higher than that of unbound daptomycin.

Webster - direct

1 Q. And how does this article by Dr. Chambers relate to
2 your opinions regarding the effects of protein binding on
3 antibiotic activity?

4 A. It illustrates quite clearly you can't make a direct
5 translation of in vitro to in vivo for this one reason as
6 well as all the other differences between the living
7 organisms in test-tubes.

8 THE COURT: Mr. Flattmann, let's take our
9 morning recess at this point.

10 MR. FLATTMANN: Yes, your Honor.

11 (Brief recess taken.)

12 THE COURT: You may proceed.

13 MR. FLATTMANN: Thank you, Your Honor.

14 BY MR. FLATTMANN:

15 Q. Dr. Webster, please turn to your Slide PDX-123. I
16 want to discuss some of the elements of the dependent claims
17 of the Ashley patents, now that we have covered the
18 independent claims.

19 What have you shown on this slide?

20 A. These are the dependent claims of the, claim elements
21 of the Ashley patents as they relate to Mylan's label.

22 Q. Let's go to the first row. What is your opinion
23 regarding whether Mylan's product meets the element
24 doxycycline or a pharmaceutically acceptable salt in Claims
25 12 to 15 of the '267 patent?

Webster - direct

1 A. The label says that the active ingredient is
2 doxycycline. So, yes, it meets that claim.

3 Q. What is your opinion regarding whether Mylan's
4 product meets the element hydrates of doxycycline and the
5 element doxycycline monohydrate?

6 A. The active ingredient in the label is doxycycline
7 monohydrate.

8 Q. Therefore?

9 A. Therefore, it infringes.

10 Q. What is your opinion regarding whether Mylan's
11 product meets the element acne rosacea in Claim 22 of the
12 '267 patent?

13 A. Their label says it is indicated for the papules and
14 pustules of rosacea.

15 So it meets that claim element.

16 Q. What is your opinion regarding whether Mylan's
17 product meets the element the lesions are pustules and
18 papules in Claims 26 and 30 of the '236 patent?

19 A. The wording in Mylan's label says indicated for
20 papules and pustules of rosacea.

21 Q. Therefore?

22 A. Therefore, it infringes.

23 Q. What is your opinion whether Mylan's product meets
24 the Element 40 to 70 percent of the antibacterial effective
25 amount in Claim 23 of the '267 patent?

Webster - direct

1 A. The label says 40 milligrams doxycycline dosage
2 strength, which is 40 percent of a hundred milligrams. So
3 it meets that element.

4 Q. What is your opinion whether Mylan's product meets
5 the element administered in an amount of 40 milligrams in
6 Claims 14, 15, 23 and 26 of the '572 patent?

7 A. The Mylan label says 40 milligrams doxycycline dosage
8 strength indicated for once-daily administration. So it
9 meets that.

10 Q. Now, I want to talk about the element administered by
11 sustained release in Claims 15 and 24 of the '572 patent.
12 First of all, how has that term been construed in this case?

13 A. That it is administered by a method of drug delivery
14 to achieve a certain level of the drug over a period of
15 time.

16 Q. And what is your opinion regarding whether Mylan's
17 product is to be administered by a method of drug delivery
18 to achieve a certain level of the drug over a period of
19 time?

20 A. Their label reads 30 milligrams immediate release,
21 ten milligrams delayed release. So it meets that element.

22 Q. What is your opinion regarding whether Mylan's
23 product meets the element administered once a day in Claim
24 26 of the '572 patent?

25 A. The Mylan label reads indicated for once-daily

Webster - direct

1 administration, so it meets that element.

2 Q. I think we have now covered all the elements of all
3 the asserted claims.

4 In summary, in your opinion, does Mylan infringe
5 all of the asserted claims of the Ashley patent?

6 A. Yes, Mylan infringes all of the asserted claims.

7 Q. Have you formed an opinion as to whether the claims
8 of the Ashley patent are valid?

9 A. The claims are valid.

10 Q. Please turn to the next slide in your binder, it is
11 PDX-124.

12 How would you summarize your opinion concerning
13 validity here?

14 A. The patents are valid because no reference has been
15 supplied, that discloses each and every element of the
16 asserted claims, and none of the asserted claims of the
17 Ashley patent are obvious.

18 Q. Let's take those in part. Have you formed an opinion
19 as to whether any of the art cited by Mylan's expert
20 discloses each and every element of the asserted claims of
21 the Ashley patents, either expressly or inherently?

22 A. No reference discloses each and every element.

23 Q. And what did you consider in forming that opinion?

24 A. I considered the references provided by Mylan.

25 Q. What is the basis for your opinion that none of the

Webster - direct

1 asserted claims of the Ashley patents are obvious over the
2 art that Mylan cites?

3 A. None of them are obvious because they don't deal with
4 sub-antimicrobial tetracyclines and specifically
5 sub-antimicrobial doxycycline.

6 Q. First let's look at the Pflugfelder reference, which
7 is in your book at DTX-1045. Have you reviewed DTX-1045?

8 A. I have.

9 Q. What is your opinion as to whether Pflugfelder
10 renders obvious any claims of the '267 or '572 patent?

11 A. Pflugfelder does not render obvious any of the
12 claims. It's really a patent talking about treating
13 meibomian gland disease in the eye, which is distinct.

14 Q. Please turn to the next slide in your binder, which
15 is PDX-125. What have you shown here?

16 A. Pflugfelder discloses he treated meibomian gland
17 disease. Meibomian gland is an altered sebaceous gland in
18 the rim of the eyelid that makes a tear film protectant.
19 The corners of the tear film prevents it from evaporating
20 and protects the cornea and the inner part of the eyelid.

21 Q. What causes meibomian gland disease?

22 A. We don't know.

23 Q. What is the relationship between meibomian gland
24 disease and skin rosacea?

25 A. Patients with rosacea may have it or they may not.

Webster - direct

1 And vice versa, patients with meibomian gland disease may
2 have rosacea or may not.

3 Q. Are meibomian gland disease and skin rosacea distinct
4 disease states?

5 A. Yes, they are.

6 Q. If a drug is shown to be effective for the treatment
7 of meibomian gland disease, what would be a person of
8 ordinary skill's expectation be as to whether that same drug
9 would also be effective for treating skin rosacea?

10 A. A person of ordinary skill would think it was an eye
11 disease and not a skin disease and that drug would not be
12 effective.

13 Q. Please turn to the next slide in your binder,
14 PDX-126. What have you shown here?

15 A. Pflugfelder does not disclose at least the following
16 claim elements.

17 Q. In your view, what elements of the claims are not met
18 by the disclosure of Pflugfelder?

19 A. In the '267 patent, a method of treating acne that
20 results in the lesion count wherein the lesions are pustules
21 and papules. In the '572 patent, similarly, a method for
22 treating papules and pustules of rosacea in an amount that
23 is effective to treat the papules and pustules of rosacea.

24 Q. Can you please summarize your view as to why the
25 asserted claims are not obvious in view of Pflugfelder?

Webster - direct

1 A. Pflugfelder is not talking about rosacea.

2 Q. Please turn in your witness book to Exhibit PTX-478.

3 What is it?

4 A. This is a notice of allowability.

5 Q. Could you please speak up, Doctor?

6 A. This is a notice of allowability.

7 Q. What patent does it relate to?

8 A. It relates to the rosacea patent.

9 Q. Did you consider this notice of allowability in
10 forming your opinions as to whether the Ashley patents are
11 valid in light of Pflugfelder?

12 A. I did.

13 MR. FLATTMANN: Your Honor, I offer PTX-478 into
14 evidence.

15 MR. STEUER: No objection.

16 THE COURT: It is admitted.

17 (Plaintiffs' Trial Exhibit No. 478 received in
18 evidence.)

19 BY MR. FLATTMANN:

20 Q. Please turn to Page 3 of PTX-478. Are you there?

21 A. I am.

22 Q. How does this page from the patent examiner relate to
23 your opinions regarding the Pflugfelder patent?

24 A. It shows first that the examiner was aware of the
25 Pflugfelder patent, and considered that the closest prior

Webster - direct

1 art, which they said was Pflugfelder, teaches a method for
2 treating meibomian gland disease associated with rosacea.
3 Pflugfelder, however, they say, does not explicitly teach a
4 method for treating papules and pustules of rosacea by
5 orally administering an antibiotic tetracycline compound in
6 an amount which results of 10 to 80 percent.

7 Q. Do you agree with the patent examiner?

8 A. I do.

9 Q. Will you please turn to the next slide in your
10 binder, PDX-127. What have you shown here?

11 A. This is the reference to Dr. Gilchrest.

12 Q. What is your opinion as to whether any of these
13 remaining six references disclose each and every element of
14 the asserted claims of the Ashley patents, either expressly
15 or inherently?

16 A. None of them describe each and every element of the
17 Ashley patents.

18 Q. Why is that your opinion?

19 A. They don't discuss the sub-antibacterial amount.
20 They discuss an amount -- do not discuss an amount that
21 results in no reduction of skin microflora. They don't use
22 doxycycline in an amount of 40 milligrams and in fact don't
23 consider doxycycline or tetracycline as anything other than
24 an antibiotic.

25 Q. Please turn to the next slide in your binder,

Webster - direct

1 PDX-128. What have you shown here?

2 A. These are some of the references that were cited,
3 that fail to discuss the sub-antibacterial amount.

4 Q. What is the basis of your opinion that these six
5 Gilchrest references that were listed on the prior slide do
6 not disclose the elements of sub-antibacterial amount?

7 A. It is not discussed, ever.

8 Q. Which if any of the original Gilchrest nine
9 references expressly disclose that the amount used was
10 antibacterial?

11 A. All of them.

12 Q. Can you point out which ones?

13 A. Murphy talks about a broad spectrum of antibiotic
14 tetracycline. Knox talks about systemic antibiotic
15 treatment. Cuniffe talks about reducing phylo-colonization
16 by staphylococcus and propane bacteria, which is by
17 definition an antimicrobial agent. And Witkowski talks
18 about an antibacterial agent.

19 Q. Does Mylan, to your understanding, still rely on each
20 of those four references at the bottom of the screen,
21 Murphy, Knox, Cuniffe and Witkowski?

22 A. No, they have jettisoned Knox through Witkowski and
23 only considered Murphy.

24 Q. Murphy was mentioned by counsel in his opening
25 statement. What is your understanding of what it refers to?

Webster - direct

1 A. It refers to tetracycline in a broad spectrum
2 antibiotic mode.

3 Q. Does it suggest or disclose sub-antibiotic
4 tetracycline?

5 A. It does not.

6 Q. Please turn to the next slide in your binder,
7 PDX-129. What have you illustrated here?

8 A. This is illustrating that the phrasing
9 sub-antibacterial amount and ten to 80 percent of the
10 antibacterial effective amount are really two different
11 limitations.

12 Q. Dr. Gilchrest has pointed in the past to the fact
13 that some of the six references arguably disclose the
14 element ten to 80 percent of the antibacterial effective
15 amount. How if at all does that observation affect your
16 opinion as to whether these references disclose the element
17 sub-antibacterial or not?

18 A. They don't in any way address whether it is
19 sub-antibacterial.

20 Q. Why is that?

21 A. Ten to 80 percent is a mathematical calculation.
22 Sub-antibacterial involves testing in people to show that it
23 is truly sub-antibacterial.

24 Q. In your opinion, prior to the invention of the Ashley
25 patents, would a person of ordinary skill have had a

Webster - direct

1 reasonable expectation of success in using a
2 sub-antibacterial amount of a tetracycline compound to treat
3 acne or rosacea in view of these six references?

4 A. They would not.

5 Q. Why is that?

6 A. Because at the time it was thought that more is
7 better. Many doctors still think that. And at the time
8 rosacea in particular was thought maybe to be a bacterial
9 disease.

10 Q. More what is better?

11 A. More drug is better than less drug.

12 Q. Please turn to the next slide in your binder,
13 PDX-130. What have you shown here?

14 A. The Ashley patent claims that regard skin microflora.

15 Q. What element have you highlighted?

16 A. The drug is in an amount that results in no reduction
17 of skin microflora during a six-month treatment. In other
18 words, in-vivo testing is required.

19 Q. How was this limitation addressed by the six
20 Gilchrest references?

21 A. They don't address it at all. Reduction of skin
22 microflora doesn't come up either in thought or in deed.

23 Q. How can it be determined whether a given dose of
24 antibiotic tetracycline results in no reduction of skin
25 microflora over a six-month period?

Webster - direct

1 A. You put it in people and test it.

2 Q. Do any of the six references cited by Dr. Gilchrest
3 described any in vivo clinical microbiology studies of the
4 tetracycline compounds they administered?

5 A. They do.

6 Q. Please turn to your Slide PDX-131. What have you
7 shown here, Doctor?

8 A. Similar to the last issue, that skin microflora
9 reduction and ten to 80 percent of the antibiotic amount are
10 really separate limitations.

11 Q. And, again, Dr. Gilchrest had pointed out that some
12 of the six references arguably disclose the element ten to
13 80 percent of antibiotic amount. How if at all does that
14 observation affect your opinion that these references do not
15 disclose no reduction in skin microflora?

16 A. The references do disclose -- or fail to disclose any
17 reduction in skin microflora. And that really doesn't
18 relate to the mathematical calculation of ten to 80 percent
19 of an antibiotic dose.

20 Q. In your opinion, prior to the invention of the Ashley
21 patents, would a person of ordinary skill have had a
22 reasonable expectation of success in treating acne or
23 rosacea with a dose of tetracycline that did not result in
24 reduction of skin microflora over a six-month period?

25 A. They would not.

Webster - direct

1 Q. Why is that?

2 A. Because at the time it was thought that a higher dose
3 was a better dose, and that bacteria were involved in both
4 diseases.

5 Q. Can you explain, why did people think that a higher
6 dose was a better dose?

7 A. It doesn't make sense, that more is usually better.
8 If you use a little bit of drug, often using more is better.
9 The only experience we had with antibiotics manually was
10 treating infection, where it was clear that you didn't want
11 to throw little slaps at the bacteria. You wanted to give
12 them a good punch to kill them. It was also time-honored
13 dosing.

14 Q. Excuse me?

15 A. It was a time-honored dosing, giving full dose for
16 these diseases.

17 Q. I see. Please turn to PDX-132. What have you shown
18 here?

19 A. The patent claims regarding 40 milligrams
20 doxycycline.

21 Q. Which claims are those?

22 A. 14 and 23 in the '572 patent.

23 Q. Is the use of doxycycline disclosed in any of the six
24 Gilchrest references?

25 A. It is not.

Webster - direct

1 Q. Is the use of doxycycline in an amount of 40
2 milligrams disclosed in any of those references?

3 A. It is not.

4 Q. Is the use of any tetracycline in an amount disclosed
5 of 40 milligrams disclosed in any of those references?

6 A. It is not.

7 Q. Do you have any opinion regarding whether doxycycline
8 is functionally equivalent to other tetracycline compounds?

9 A. All the tetracyclines are distinctly different and
10 have their own characteristics, so, no, it is not
11 functionally equivalent.

12 Q. With regard, specifically, to Claims 14 and 23 of the
13 '572 patent, what is your opinion regarding whether the six
14 Gilchrest references would render these obviousness?

15 A. It would not render them obvious.

16 Q. Would you please explain why?

17 A. It doesn't talk about doxycycline or an amount of 40
18 milligrams or an amount of sub-antibacterial dosing.

19 Q. What is your opinion regarding whether the Ashley
20 patent claims would be obvious in light of the six Gilchrest
21 references that we have been talking about in combination
22 with knowledge of the drug Periostat?

23 A. Even in combination with knowledge of the drug
24 Periostat, Periostat was for treating a definite disease,
25 completely distinct, not linked in any way to acne or

Webster - direct

1 rosacea. So that knowledge would not help you.

2 Q. Now, was Periostat an anti-bacterial amount or a
3 sub-antibacterial amount?

4 A. Sub-antibacterial.

5 Q. So in light of the fact that Periostat was a
6 sub-antibacterial amount, would it have been obvious in 2000
7 to use Periostat to treat rosacea?

8 A. It wasn't obvious to me.

9 Q. Why not?

10 A. Because I thought it would take more to get the
11 disease better.

12 Q. What was your understanding concerning the perceived
13 role of bacteria in rosacea at that time?

14 A. At the time there was a lot of serious thought that
15 rosacea may be a result of an infection with bacteria in the
16 stomach. And it sounds farfetched, but there is good
17 reasoning that was behind it. Helicobacter pylori is a drug
18 that when it affects the stomach affects gastric ulcers, and
19 a Nobel Prize came out of that work. It is real serious
20 science. And some of the patients were treated for
21 Helicobacter infection because they said an ulcerative
22 rosacea and their rosacea got better. For a long time
23 dermatologists said aha, we have a disease on the face
24 caused by this infection in the stomach and isn't that
25 interesting and now we know why doxycycline works.

Webster - direct

1 Further studies in many years past, it turns out
2 you have two diseases treated by the same drug that are in
3 no way related causal-wise.

4 Q. Please turn to Plaintiffs' Trial Exhibit 399 in your
5 witness book, if you would. Do you recognize it?

6 A. I do.

7 Q. What is it?

8 A. It is a review about the role of Helicobacter pylori
9 and its eradication in rosacea.

10 Q. Who is it authored by?

11 A. It is authored by Szlachcic, Sliwowski, Karczewska,
12 Bielanski, Pyrko, Polonczyk, and Konturek.

13 Q. How does this reference relate to your opinion
14 concerning the perceived role of bacteria in rosacea as of
15 2000?

16 A. It tells what the thinking was at the time of the
17 role of Helicobacter pylori in rosacea.

18 Q. What was that opinion?

19 A. That it was causal and involved.

20 MR. FLATTMANN: Your Honor, I offer PTX-399 into
21 evidence.

22 MR. STEUER: No objection.

23 THE COURT: It is admitted.

24 (Plaintiffs' Trial Exhibit No. 399 received in
25 evidence.)

Webster - direct

1 BY MR. FLATTMANN:

2 Q. What is your opinion, Dr. Webster, concerning whether
3 in light of the six Gilchrest references, dermatologists
4 would have prescribed a 20-milligram twice-a-day dose of
5 doxycycline earlier in time except that it wasn't
6 commercially available for many years?

7 A. I think there would have been extreme skepticism.
8 There is, in fact, skepticism that remains today that 40
9 milligrams is enough.

10 Q. Can you please elaborate on that?

11 A. I give a lot of talks on continuing education in
12 rosacea and acne. Invariably, after the talk or during the
13 talks, somebody puts their hand up and says, can you really
14 tell me that 40 milligrams work? It's got to be too little,
15 and we talk about the data that it does indeed work. So the
16 skepticism remains. And it would have been even more
17 skeptical ten years ago.

18 Q. What types doses were dermatologists actually using
19 at that time in 2000?

20 A. Clearly antibacterial dosage, a hundred or 200 a day.

21 Q. Now, what do you base on view on?

22 A. Because I was around back then and many of them are
23 still doing it today.

24 Q. What if anything do the references cited by Dr.
25 Gilchrest tell a person of ordinary skill about whether 40

Webster - direct

1 milligrams a day of doxycycline is a sub-antibacterial
2 amount?

3 A. They address none of those three elements. 40
4 milligrams isn't brought up. Doxycycline is not brought up.
5 And the concept is sub-antibacterial isn't a problem.

6 Q. Let me ask you to please turn to PDX-133, if you
7 would. What have you shown here?

8 A. These are the dependent claims and the different
9 combinations of references that Mylan would use to attack them.

10 Q. In your opinion, do any of the combinations of
11 references that you have shown on this slide render obvious
12 the claims of the Ashley patent?

13 A. They do not.

14 Q. Some of these references are new to me. They
15 recently appeared on the 282 statement from Mylan. What is
16 your understanding of what the Doyon and Muhammad patents
17 disclose?

18 A. Those patents are talking about formulation of full
19 dose antibiotics for treating infections, not rosacea and
20 not low dose.

21 Q. And what is your understanding of what the Hussar and
22 Pechere references disclose?

23 A. They're talking about issues of compliance which in
24 doctor speak means patient following the directions that the
25 physician gives them. The gentler term is adherence but

Webster - direct

1 it's how well the patient is expected to do.

2 Q. What is your understanding of what the Maibach
3 reference discloses?

4 A. In Maibach's paper, he is talking about full dose
5 antimicrobial treatment with doxycycline.

6 Q. Okay. What, if anything, do any of these new
7 references say about the use of subantibacterial amounts of
8 tetracyclines to treat acne or rosacea?

9 A. Nothing.

10 Q. Okay. Let's now discuss your opinions regarding
11 Dr. Feldman's alleged treatment of a single patient with
12 Periostat prior to April of 2000. Could you turn to PDX-134
13 in your slide deck.

14 What have you shown here?

15 A. The circumstances around Dr. Feldman's treatment of a
16 single patient with Periostat.

17 Q. What is your opinion as to whether Dr. Feldman's
18 alleged prescription of Periostat publicly disclosed each
19 and every element of the asserted claims of the Ashley
20 patent?

21 A. His treatment did not disclose each and every element
22 of the asserted claims.

23 Q. Why is that your opinion?

24 A. Firstly, there is no evidence the patient took the
25 drug. Dr. Feldman kept this information private. Nobody

Webster - direct

1 knew about it, and there is no evidence the patient got
2 better from taking the drug.

3 Q. What do you mean when you say the treatment of this
4 patient was not publicly disclosed?

5 A. This was an interaction between Dr. Feldman and his
6 patient which, by medical ethics at the time and by law now,
7 is a matter that is extremely private and not for
8 dissemination in any way.

9 Q. Please turn in your exhibit book to the document,
10 Defendant's Trial Exhibit 1559.

11 Do you recognize this document?

12 A. Yes, I do.

13 Q. What is it?

14 A. This is Dr. Feldman's chart note.

15 Q. I'm sorry?

16 A. His chart note of the interaction where he says he
17 wrote for Periostat.

18 Q. Did you consider this document in forming your
19 opinions concerning Dr. Feldman's alleged use of Periostat
20 to treat this patient?

21 A. Yes, I did.

22 Q. Do you have an understanding as to whether or not
23 DTX-1559 itself is a prescription?

24 A. It is not a prescription. It is a record of his
25 interaction.

Webster - direct

1 Q. Have you ever seen any prescription for this patient?

2 A. No.

3 Q. Do you have any understanding regarding whether this
4 patient record was ever published?

5 A. It was not published.

6 Q. And how do you know that?

7 A. Dr. Feldman said so.

8 Q. Do you have any opinion as to whether or not this
9 patient record discloses each and every element of the
10 asserted claims of the Ashley patents?

11 A. It does not.

12 Q. And what is the basis for your opinion?

13 A. What I read on the paper.

14 Q. Okay. Well, for instance, does this patient record
15 disclose whether Periostat was administered orally to this
16 patient in accordance with claim 1 of the two patents?

17 A. That would be the assumption that it was administered
18 orally as a pill. We don't know it was actually
19 administered.

20 Q. And do we know whether the prescription was ever
21 filled?

22 A. We don't know whether the prescription was filled.

23 Q. Do we know if the patient was ever orally
24 administered the drug?

25 A. We don't know if the patient took the drug.

Webster - direct

1 Q. Did you consider the testimony of Dr. Feldman
2 regarding whether Periostat was ever orally administered to
3 the patient?

4 A. He said he didn't know if the patient ever took it in
5 his testimony.

6 Q. Please turn to the next slide in your binder,
7 PDX-135.

8 What have you shown here?

9 A. I have shown what Dr. Feldman doesn't know about this
10 interaction, specifically, whether the patient ever filled
11 the prescription, and if they filled it, whether they ever
12 took it.

13 Q. In your experience, do patients always take the
14 medicine that is prescribed to them?

15 A. No, they clearly do not always take the medicine as
16 prescribed.

17 Q. What are the reasons for that?

18 A. They may think it costs too much. They may not want
19 to take another pill. They may just not want to do it.

20 Q. All right. Please turn to PDX-136.

21 And what have you shown here?

22 A. This is referring to the IMS data on the prescription
23 of Periostat.

24 Q. Okay. And what is IMS data?

25 A. IMS is a service that monitors prescribing activities

Webster - direct

1 of doctors. It tracks what doctors write what drugs.

2 Q. And what does the IMS data in this case say about of
3 a patient's names, ages or genders?

4 A. No identifying characteristic of a patient is
5 included in the IMS data.

6 Q. What does the IMS data say about the patient's
7 diagnoses?

8 A. It says nothing about the diagnoses.

9 Q. What does the IMS say what indications?

10 A. It doesn't say anything.

11 Q. What does the IMS data say whether any particular
12 patient took the Periostat actually prescribed to them?

13 A. It doesn't.

14 Q. What does the IMS data say regarding Dr. Feldman's
15 patient who is the subject of the patient record that we
16 were just looking at?

17 A. It doesn't indicate whether any Periostat was taken
18 prior to 2008.

19 Q. Does it say whether this particular patient took
20 Periostat?

21 A. We know nothing about this particular patient.

22 Q. And, in your opinion, does the patient record
23 disclose whether Periostat actually reduced lesion count in
24 this patient in accordance with the claims of the Ashley
25 patent?

Webster - direct

1 A. It does not. It merely records Dr. Feldman
2 recommended it, and we don't know if the patient took it or
3 if they got better.

4 Q. And in forming that opinion, did you consider
5 Dr. Feldman's testimony?

6 A. I did.

7 Q. What did he say about it?

8 A. He said the same thing.

9 Q. All right. Please turn to the next slide in your
10 binder PDX-137.

11 Okay. Why do you rely on this testimony from
12 Dr. Feldman?

13 A. Well, the reduction of lesion count is an important
14 issue, and Dr. Feldman doesn't know whether Periostat
15 reduced the lesion count.

16 Q. In your experience, did Dr. Feldman testify as to
17 whether there was a follow-up visit for this patient or not?

18 A. There was not a follow-up visit.

19 Q. In your experience, if a patient doesn't return for a
20 follow-up visit, do you assume that the treatment was
21 successful?

22 A. If anything, you assume otherwise. If a drug works,
23 patients want more of it.

24 Q. In summary, in your opinion, does the patient record
25 disclose whether the patient engaged in a method of treating

Webster - direct

1 acne or a method of treating the papules and pustules of
2 rosacea?

3 A. There is no evidence the patient engaged in any of
4 that in the office notes.

5 Q. In your opinion, does the patient record disclose
6 whether Periostat was actually administered long term to
7 this patient in accordance with the claims of the Ashley
8 patents?

9 A. We no idea if the patient took the medicine at all,
10 short term or long term.

11 Q. From Dr. Feldman's testimony, what was your takeaway
12 concerning whether Periostat was administered long term?

13 A. I have to conclude that it wasn't.

14 Q. Why?

15 A. There is no evidence saying that it was.

16 Q. Okay. Now, Dr. Gilchrest talks about how the patient
17 record discusses a prescription of 180 Periostat pills with
18 one refill. Does that notation change your opinion at all
19 regarding whether Periostat was administered long term to
20 this patient?

21 A. It doesn't address it.

22 Q. Okay. Why not?

23 A. You still don't know if the patient took it or filled
24 it.

25 Q. Does the patient record say anything about whether

Webster - direct

1 the patient was taking bisphosphonate compounds?

2 A. It doesn't say anything about that.

3 Q. Does it say whether there was any reduction of skin
4 micro flora during a six-month treatment?

5 A. There was no follow-up treatment and certainly no
6 testing.

7 Q. What did you ultimately conclude about this patient?

8 A. That you can find nothing relevant to this case.

9 Q. Please turn to the next slide in your binder,
10 PDX-138.

11 What are you showing here?

12 A. This is the -- Dr. Feldman's treatment was clearly
13 not a public use.

14 Q. How did you reach that conclusion?

15 A. Well, Dr. Feldman said that the patient record was
16 kept in a locked storage facility, and he said that he
17 didn't disclose it prior to this litigation. He didn't
18 publish it or discuss with others, his alleged prescribing
19 of Periostat.

20 And I have every reason to believe this is true
21 not only because he said it but because if he did disclose
22 it with identifying characteristics, it would have been a
23 clear ethical violation.

24 Q. Can you explain that?

25 A. A doctor/patient relationship is a private thing, and

Webster - direct

1 your details are not supposed to be spread around.

2 Q. So, in your opinion, was Dr. Feldman's alleged
3 prescribing of Periostat to this patient known to one of
4 ordinary skill in the art as of April 2000?

5 A. It was known to nobody.

6 Q. In your opinion, was the patient record for
7 Dr. Feldman's alleged patient available to one of skill in
8 the art as of April 2000?

9 A. It was not.

10 Q. I'd now like to discuss your opinions concerning
11 Dr. Feldman's alleged personal use of Periostat prior to
12 April of 2000. Can you please turn to slide PDX-139?

13 What have you shown here, doctor?

14 A. That Dr. Feldman's alleged personal use did not
15 publicly disclose each and every element of the asserted
16 claims.

17 Q. And was it a personal or private use in your opinion?
18 I'm sorry. Was it a private or public use in your opinion?

19 A. It was a private use.

20 Q. How do you know that?

21 A. He said so.

22 Q. What was Periostat allegedly prescribed to
23 Dr. Feldman for?

24 A. For gum disease.

25 Q. Please turn to the next slide in your binder,

Webster - direct

1 PDX-140.

2 What have you shown here?

3 A. The elements of claim 1 of the Ashley patents are not
4 met by Dr. Feldman's personal use.

5 Q. What is your view concerning whether Dr. Feldman's
6 alleged personal use meets the limitation, reduces lesion
7 count?

8 A. There is no recorded lesion counts.

9 Q. Why not?

10 A. One has to presume he didn't do them.

11 Q. All right. And why is it your opinion that
12 Dr. Feldman's alleged personal use does not meet the
13 limitation amount that results in no reduction of skin
14 microflora during a six-month treatment?

15 A. He did no testing of skin microflora.

16 Q. To what extent was Dr. Feldman's personal use
17 discussed with others?

18 A. It wasn't discussed.

19 Q. To what extent was Dr. Feldman alleged personal use
20 published at all?

21 A. It was not published.

22 Q. How do you know that?

23 A. He said so in his testimony.

24 Q. Has anyone else other than Dr. Feldman come forward
25 with any evidence that he actually took Periostat for his

Webster - direct

1 own rosacea?

2 A. No.

3 Q. Have you seen any documents whatsoever other than his
4 deposition in this case suggesting that he took Periostat
5 for his rosacea?

6 A. No.

7 Q. Were any patient records regarding Dr. Feldman's
8 personal use available to a person of skill in the art as of
9 April 2000?

10 A. No.

11 Q. Are you aware of any way in which Dr. Feldman's
12 alleged personal use was made public?

13 A. No.

14 Q. What does the patient record for Dr. Feldman's
15 patients say about the mode of administration?

16 A. It's presumed to be oral.

17 Q. Okay. Well, what do we know about whether the
18 patient actually took it orally?

19 A. We don't know that.

20 Q. And was it prescribed as a once daily or twice daily
21 dosage?

22 A. Twice daily.

23 Q. And what did Dr. Feldman say about his own alleged
24 dose of doxycycline? Was it once or twice?

25 A. Twice.

Webster - direct

1 Q. Okay. Now, what is your opinion regarding whether
2 Dr. Feldman's alleged personal use of Periostat or his
3 alleged patient's use would have rendered obvious any of the
4 asserted claims as of April of 2000?

5 A. This was, if it happened, a secret use, not public.
6 It didn't record decrease in papules and pustules, and it
7 didn't address skin microflora, so it really meets none of
8 the elements we're talking about.

9 Q. To what extent were any of the alleged uses known to
10 a person of ordinary skill in the art at that time?

11 A. They were completely unknown.

12 Q. In all of your years as a practicing dermatologist,
13 had you ever heard about Dr. Feldman's use of Periostat to
14 treat rosacea?

15 A. No.

16 Q. When was the first time?

17 A. Only through this trial.

18 Q. Now, Dr. Stafford opines that Periostat IMS data
19 demonstrates that other dermatologists were prescribing
20 Periostat for rosacea in April of 2000. Do you agree?

21 A. I agree. Oh. For rosacea, they were prescribing?
22 You don't know what they were prescribing.

23 Q. Have you relied on the data Dr. Stafford relies on?

24 A. I have.

25 Q. What does that data say about the diagnosis for any

Webster - direct

1 of the patients for which the drug was prescribed?

2 A. IMS data says nothing about the reason for
3 prescription.

4 Q. Okay. And does it reveal any patient names?

5 A. It doesn't reveal patient names.

6 Q. And does it reveal any patient names?

7 A. It doesn't reveal patient names, no.

8 Q. In your opinion, does that Periostat IMS data that
9 Dr. Stafford relies on show there was any public use of the
10 claimed invention of the Ashley patents prior to April of
11 2000?

12 A. It doesn't. It doesn't show at all why they would
13 prescribe the drug. In the course of the week I prescribe
14 plenty of drugs that have no dermatological use. I renew
15 blood pressure medicines, I renewed patients' Viagra. In
16 the past I have renewed their Periostat for gum disease.
17 So...

18 Q. To be clear, what, if anything, does this IMS data
19 says about whether Periostat was prescribed for rosacea in
20 April 2000?

21 A. Absolutely nothing.

22 Q. Please turn to the next slide in your binder, it's
23 PDX-141. What have you shown here?

24 A. I have shown that there are some objective indicators
25 of nonobviousness for Oracea.

Webster - direct

1 Q. What don't we takes these one at a time. Have you
2 determined whether there was a long felt unmet need for the
3 patented invention?

4 A. There clearly was a long felt unmet need. I felt it
5 myself. Rosacea is a common disease that lasts all year
6 long and full dose doxycycline is a drug you can't give
7 during the summer.

8 Full dose doxycycline also causes a lot of
9 gastric upset in certain patients. And Oracea does neither
10 of these. So it has allowed me to take better care of my
11 patients and have them do it more comfortably.

12 Q. Do you attribute any unexpected properties to the
13 invention of the asserted claims?

14 A. Well, you know, it's surprising that Oracea works in
15 the dose that it does. I am still a little amazed that a
16 piddling amount of drug can do as much as it does in the
17 inflammation of rosacea. Doxycycline is a remarkable drug.

18 Q. And have you formed any opinion as to whether the
19 inventions of the asserted claims have been commercially
20 successful?

21 A. They have been very commercially successful. There
22 is a lot of drug that has been sold.

23 Q. To what do you attribute that commercial success?

24 A. It meets a need.

25 Q. And have you formed an opinion as to whether Oracea

Webster - direct

1 is covered by the claims of the Ashley patents?

2 A. It is.

3 Q. How did you form an opinion?

4 A. By reading the claims and reading the package insert
5 for Oracea.

6 Q. And how did these factors, long-felt unmet need,
7 unexpected properties and commercial success that you have
8 described, influence your opinion regarding nonobviousness?

9 A. Well, they reinforced it, and maybe the most
10 important nonobvious factor is I didn't patent it myself,
11 which is a source of ongoing embarrassment.

12 Q. In summary, as an expert in the field of dermatology,
13 with decades of experience in treating rosacea, what is your
14 opinion regarding whether any of the art or the alleged
15 public uses cited by Mylan render anticipated or obvious any
16 of the asserted claims of the Ashley patent?

17 A. They do not render anticipated or obvious.

18 Q. Please explain why not?

19 A. Because none of them showed doxycycline in the amount
20 of 40 milligrams reducing papules and pustules of rosacea
21 and not affecting bacterial amount in vivo.

22 MR. FLATTMANN: Thank you very much, Doctor. I
23 have no further questions.

24 THE COURT: Thank you.

25 Cross-examination.

Webster - cross

1 MR. STEUER: Thank you, Your Honor.

2 CROSS-EXAMINATION

3 BY MR. STEUER:

4 Q. Good morning, Dr. Webster. My name is David Steuer.

5 We haven't had the pleasure of being together before.

6 Dr. Webster, you have had a long relationship
7 with Galderma and before that CollaGenex. Isn't that
8 correct?

9 A. That is.

10 Q. And you have given speeches for Galderma. Correct?

11 A. I tend not to give speeches for companies. I tend to
12 give speeches about diseases the companies may sponsor.

13 Q. Did you tell us at your deposition you gave about
14 five speeches for Galderma?

15 A. Over the years I probably have done that, in that
16 sense.

17 Q. And that you get about \$2,000-plus expenses a speech?

18 A. Something like that.

19 Q. And you have spent a few years on the scientific
20 advisory board of CollaGenex. Correct?

21 A. Correct.

22 Q. And there is an annual stipend of about \$20,000 a
23 year for that?

24 A. Something like that.

25 Q. In fact, you were quite aware of the development of

Webster - cross

1 Oracea, isn't that correct, as a member of the scientific
2 advisory board?

3 A. Yes.

4 Q. In fact, from time to time you offered advice to
5 people that were working on that project. Isn't that
6 correct?

7 A. Correct.

8 Q. Now, Dr. Webster, you are not board certified in
9 infectious diseases. Correct?

10 A. Correct.

11 Q. And you are not an expert in pharmacokinetics.
12 Correct?

13 A. Correct.

14 Q. And you are not an expert in pharmacodynamics?

15 A. Correct.

16 Q. I want to talk about your comments about dosing
17 practices before the invention, before the Ashley invention.
18 On direct you said that before Ashley, rosacea was dosed in
19 the way you would dose an antibiotic infection. Is that
20 right?

21 A. That's what I was taught and what I practiced and
22 what others did.

23 Q. That's what you practiced and that would be 100 to
24 200 milligrams a day?

25 A. Correct.

Webster - cross

1 Q. In fact, before the Ashley patent wasn't it common
2 practice among dermatologists such as yourself to dose acne
3 patients with 50 or a hundred milligrams of doxycycline once
4 or twice a day?

5 A. That would have been a low dose for acne. It was not
6 common practice.

7 Q. It was your practice, though. Wasn't it?

8 A. No, it wasn't.

9 MR. STEUER: Your Honor, I would like to offer
10 for impeachment Defendants' Trial Exhibit 2321.

11 THE COURT: Okay.

12 MR. STEUER: May I approach, Your Honor?

13 THE COURT: You may.

14 BY MR. STEUER:

15 Q. Dr. Webster, do you see Exhibit 2321?

16 A. Yes.

17 Q. Do you recognize it?

18 A. I do.

19 Q. Is it an article you wrote?

20 A. It is.

21 MR. STEUER: Your Honor, I offer Exhibit 2321.

22 THE COURT: Any objection?

23 MR. FLATTMANN: No objection.

24 THE COURT: It's admitted.

25 (Defendants' Exhibit No. 2321 received in

Webster - cross

1 evidence.)

2 BY MR. STEUER:

3 Q. I would like you to turn, if you would, to the page
4 at the bottom that says, in the bottom right-hand corner it
5 says V:10.3. Do you see that?

6 A. I do.

7 Q. Could you put that up. Could you highlight that box
8 right there?

9 Just to be clear, this is an article that you
10 published in 1996. Is that right?

11 A. Somewhere around there.

12 Q. And in this article you were giving advice to the
13 profession on how to treat acne. Right?

14 A. Yes.

15 Q. And in this box here that you prepared, you said the
16 commonly used treatments include doxycycline at 50 to a
17 hundred milligrams, QD to BID?

18 A. Those were the dosages available of the drug at the
19 time.

20 Q. Those were commonly used treatments, as you wrote at
21 the time?

22 A. The higher doses were commonly used.

23 Q. Is that -- did you write inaccurately there?

24 A. I believe that 50 to a hundred QD to BID was inserted
25 by the publisher because of the available dosages. I don't

Webster - cross

1 think anybody was giving 50 a day and getting any better.

2 It certainly was not my intent.

3 Q. It is your belief that it slipped by you, by the
4 publisher, or it wasn't reviewed by --

5 A. Things change between the galley proofs and the file
6 or between the manuscript and the galleys.

7 Q. And QD, that means once a day. Right?

8 A. Yes.

9 THE COURT: Dr. Webster, you have to let each
10 other complete what you are saying so we can get a complete
11 transcript of this.

12 Go ahead.

13 BY MR. STEUER:

14 Q. I think we had an answer that QD means once a day?

15 A. Yes.

16 Q. And BID means twice a day?

17 A. Yes?

18 Q. So if I were to translate the abbreviations there to
19 English the line would say, doxycycline 50 to 100 milligrams
20 once a day to twice a day. Right?

21 A. Right.

22 Q. And, in fact, in this article, you said that you like
23 to prescribe doxycycline. Correct?

24 A. Yes.

25 Q. And one of the reasons was that it was significantly

Webster - cross

1 less expensive than other antibiotics. Correct?

2 A. Specifically administered.

3 Q. You can take that down.

4 One of the reasons, this was generic doxycycline
5 that you were prescribing at the time. Is that right?

6 A. I assume it was available at the time if it was
7 cheaper.

8 Q. In fact, in the 1990s, you thought that a hundred
9 milligrams of tetracycline every other day may be effective
10 for the treatment of acne or rosacea. Isn't that correct?

11 A. I don't recall.

12 Q. So that would be once every two-day dosing of a
13 hundred milligrams of doxycycline, do you recall
14 recommending that?

15 A. If I recommended that, that still would be an
16 antimicrobial dosage, just given infrequently.

17 Q. Dr. Webster, you also note in the 1990s before the
18 invention that the primary effect of tetracycline with
19 respect to rosacea was anti-inflammatory. Correct?

20 A. I don't think anybody knew.

21 Q. And you didn't know that?

22 A. We still don't know convincingly what the cause of
23 rosacea is. We think we are pretty close to it.

24 Q. But it was your belief in the 1990s that the primary
25 effect of tetracycline was anti-inflammatory in the

Webster - cross

1 treatment of rosacea. Correct?

2 A. That is probably true.

3 Q. I believe you stated on direct that you were amazed
4 that rosacea could be treated with a sub-antibacterial dose
5 of doxycycline. Is that right?

6 A. I was amazed that so low a dose which happens to be
7 sub-antibacterial remained effective.

8 Q. In fact, you were aware in the 1990s that because the
9 primary effect of tetracycline in the treatment of rosacea
10 was anti-inflammatory, low doses of tetracycline may well be
11 effective. Isn't that right?

12 A. I actually published data to the contrary. There is
13 published anti-granuloma activity of the different
14 tetracycline and it was found that if you extrapolated the
15 in-vitro to the in-vivo dosage, which has all kinds of
16 limitations, it would have required the full oral dosage of
17 tetracycline to have the anti-inflammatory effect in vitro.

18 Q. So that wasn't your belief, that low doses of tet --

19 A. Certainly not in the meibomian gland situation that I
20 was discussing, which relates to both acne and to rosacea.

21 Q. You don't recall telling people that you believed
22 that low doses of tetracycline would be effective because of
23 their anti-inflammatory properties?

24 A. When I was talking about low, I wasn't talking about
25 40 milligrams. I was talking about full antibiotic dose.

Webster - cross

1 Q. Okay. Well, let me introduce for impeachment 2323.

2 MR. STEUER: May I approach?

3 THE COURT: You may approach freely.

4 MR. STEUER: Your Honor, I think I jumped ahead.

5 I would like to approach with 2322 if I may?

6 THE COURT: You may approach.

7 BY MR. STEUER:

8 Q. Dr. Webster, let's look at 2322. Do you recognize
9 this?

10 A. No.

11 Q. You don't. All right.

12 A. I believe that I wrote it. But I don't recognize it.

13 Q. It says that it's by Guy F. Webster, M.D., Ph.D.?

14 A. That would be me.

15 Q. It has an address for where to get reprint requests.
16 It's in Philadelphia, addressed to Guy F. Webster. Is that
17 an address that you could ever be reached at?

18 A. That was my address.

19 Q. Do you have any reason to believe you didn't write
20 this?

21 A. I have no reason to believe I didn't write this.

22 MR. STEUER: Your Honor, I would offer DTX-2322.

23 MR. FLATTMANN: No objection.

24 THE COURT: It is admitted.

25 (Defendants' Trial Exhibit No. 2322 received in

Webster - cross

1 evidence.)

2 BY MR. STEUER:

3 Q. Let me ask you to turn to, if you would, to the page
4 in the document, I think it's the seventh page in the
5 document. It says P-1153 near the top.

6 A. Yes.

7 Q. And it talks about therapy?

8 A. Yes.

9 Q. Do you see that? If you could highlight the last
10 sentence of the first paragraph there.

11 It says, Because tetracyclines work primarily as
12 anti-inflammatory agents in rosacea, low doses, for
13 instance, 100 milligrams every other day, may be effective?

14 Do you see that?

15 A. I do.

16 Q. And that was your belief when you wrote this article?

17 A. Yes.

18 Q. This article is from 1998. Is that right?

19 A. Yes.

20 Q. And so a hundred milligrams every day would give you,
21 that would be -- how would that compare to a 50-milligram
22 once-a-day treatment?

23 A. It would be much higher than 50 milligrams once a
24 day. It would be a decidedly antimicrobial amount.

25 Q. Why wouldn't an antimicrobial treatment be a hundred

Webster - cross

1 milligrams every day?

2 A. You can have antimicrobial effect from one dosage.

3 Q. In fact, doesn't the labeling for antimicrobial
4 agents to treat infection say that the patient should be
5 treated every day with the maintenance dose?

6 A. You are separating the idea of treating an infection
7 from having an effect on the microflora. One dosage that
8 reaches antimicrobial effect, while inadequate to treat an
9 infection, could still alter the normal flora and have
10 changes induced therein.

11 Q. Would you agree with me that this is not how you
12 would treat an infection?

13 A. I would not treat an infection that way.

14 Q. Actually, if you look ahead to the paragraph right
15 above ocular rosacea, the first line there, it says as many
16 as 50 percent of rosacea patients may have ocular complaints
17 related to the disease. Does that sound about right?

18 A. That's what it says.

19 Q. Do you still believe that?

20 A. Ocular rosacea and meibomian gland disease are
21 related to rosacea but they are not facially rosacea.

22 Q. I just ask if you agreed with the statement you made
23 in 1998.

24 A. Yes, I believe that.

25 Q. Now, it is your opinion that Oracea does not

Webster - cross

1 significantly inhibit the growth of microorganisms.

2 Correct?

3 A. Yes.

4 Q. You would agree that to infringe the Ashley patents
5 it must be shown that the Mylan ANDA product not
6 significantly inhibit the growth of microorganisms.

7 Correct?

8 A. Correct.

9 Q. And conversely, if it is not proven that the Mylan
10 ANDA product does not significantly inhibit the growth of
11 microorganisms limitation, there is no infringement of the
12 Ashley patents. Correct?

13 A. Would you repeat that?

14 Q. Yes. If it is not proven that the Mylan product does
15 not significantly inhibit the growth of microorganisms, in
16 that event, there would be no infringement. Correct?

17 A. If it is not proven?

18 Q. Yes.

19 A. If you fail to prove that the Mylan product doesn't
20 inhibit microorganisms -- there is a little too many
21 negatives there. Could you break it down?

22 Q. I am trying to quote the patent, obviously. But
23 generally speaking, if Galderma is unable to prove that
24 there is no significant antibiotic effect, then there is no
25 infringement. Right?

Webster - cross

1 A. I am still confused.

2 Q. Galderma has to show no significant antibiotic effect
3 in order to prevail on infringement. Right?

4 A. Galderma has to show that the Mylan product has no
5 significant, yes.

6 Q. Now, the limitation that the product does not
7 significantly inhibit the growth of microorganisms is not
8 limited to any particular subset of microorganisms. Is that
9 your understanding?

10 A. I think it would be limited to those that are present
11 in the human body.

12 Q. It's not limited to any specific microorganisms in
13 the human body. Correct?

14 A. I see no limitation.

15 Q. Do you see any limitation in the patent, limitation
16 that we have discussed that limits it to any particular area
17 or subset of human body locations?

18 A. No, I don't.

19 Q. Now, we talked about two studies that observed the
20 effects of 20 milligrams doxycycline taken twice daily.
21 Correct?

22 A. Correct.

23 Q. And we could call those the Skidmore and the Walker
24 2005 studies?

25 A. Yes.

Webster - cross

1 Q. None of the studies, neither of these studies
2 actually studied once-a-day Oracea. Correct?

3 A. Correct.

4 Q. And both studies used Periostat BID for the
5 doxycycline arm. Right?

6 A. Yes. The FDA said that was a similar antibiotic
7 exposure.

8 Q. Periostat is orally administered. Correct?

9 A. Yes.

10 Q. Periostat provides a 40 milligram daily dose of
11 doxycycline?

12 A. Correct.

13 Q. And you believe Periostat contains a sub-antibiotic
14 amount of doxycycline. Correct?

15 A. When given as two twenties twice a day.

16 Q. So you don't know whether Periostat is effective in
17 reducing papules and pustules of rosacea?

18 A. I don't know of a study that addresses that.

19 Q. Do you have a belief?

20 A. I believe it probably does.

21 Q. Periostat is well tolerated. Would you agree with
22 that?

23 A. Yes, it is.

24 Q. And Periostat has a long term safety profile?

25 A. It does.

Webster - cross

1 Q. Now, Walker 2005, which is Defendant's Trial
2 Exhibit 1334 -- I think we admitted that -- sought to
3 examine bacterial changes in the vagina and intestinal
4 tract; correct?

5 A. Correct.

6 Q. And Walker 2005 compared to Periostat to placebo;
7 correct?

8 A. I don't know. What number was it?

9 Q. Defendant's Trial Exhibit 1344. DTX.

10 A. Is there another number it might be? 1344 you are
11 saying?

12 Q. Yes. It's in the little binder I gave you. It
13 should be in the binder I gave you, doctor.

14 A. I'm not seeing it. Is this DTX?

15 Q. You do not have a binder?

16 A. I have a binder.

17 Q. I think it's the wrong binder.

18 (Binders passed forward.)

19 THE COURT: I don't believe we have that binder
20 either, Mr. Steuer.

21 MR. STEUER: I'm sorry, your Honor.

22 THE COURT: Do you have a second copy?

23 MR. STEUER: I have another one, yes. I was
24 given the copies to distribute and failed to obey. I'm
25 sorry.

Webster - cross

1 THE COURT: Thank you.

2 (Binders passed out.)

3 BY MR. STEUER:

4 Q. Now, I hope you have DTX-1344.

5 A. I do.

6 Q. So Walker compared Periostat to placebo; is that
7 correct?

8 A. Yes.

9 Q. Walker determined that no conclusion could be drawn
10 from the vagina portion of the study because they didn't
11 have enough patients at the end of the study; correct?

12 A. Show me where it says that, please. Is this on page
13 1166?

14 Q. I believe on 1168. If you look at the bottom of the
15 first column, the author says, starting at the last line,
16 the first column: Although the number of samples was too
17 low to provide a conclusive answer.

18 A. Yes, I've got that.

19 Q. Okay. Does that refresh your recollection that the
20 authors determined that there could be no determination
21 conclusively as to whether there was an antibiotic effect in
22 the vagina samples they took?

23 A. They said they didn't see any but they needed more
24 data to make it more conclusive.

25 Q. With respect to the intestinal tract Walker sampled

Webster - cross

1 fecal stool; correct?

2 A. Correct.

3 Q. And other than fecal stools and statistically low
4 number of vaginal swabs, Walker 2005 sampled no organs or
5 other body parts or locations for bacterial inhibition; is
6 that right?

7 A. Those were the two that they sampled.

8 Q. So that's correct?

9 A. Yes.

10 Q. And you are aware that doxycycline is largely
11 absorbed in the upper GI system; is that correct?

12 A. That's correct.

13 Q. Walker 2005 did not use a positive control; correct?

14 A. Meaning what?

15 Q. Meaning an antibiotic dose of doxycycline to see what
16 the results would be.

17 A. They did not.

18 Q. Skidmore also compared Periostat to placebo; isn't
19 that right?

20 A. Correct.

21 Q. And that's Defendant's Trial Exhibit 1018.

22 Do you have that?

23 A. I do.

24 MR. STEUER: Your Honor, I would move actually
25 Defense Trial Exhibit 1344 into evidence.

Webster - cross

1 MR. FLATTMANN: No objection.

2 THE COURT: It's admitted.

3 (DTX No. 1344 received into evidence.)

4 MR. STEUER: And I move Defendant's Trial
5 Exhibit 1018 into evidence.

6 MR. FLATTMANN: No objection.

7 THE COURT: It's admitted.

8 (DTX No. 1018 received into evidence.)

9 BY MR. STEUER:

10 Q. Now, Skidmore only looked for bacterial changes on a
11 two centimeter square skin between the eyebrows; is that
12 correct?

13 A. That is the standard way of doing that on the skin.

14 Q. Is that correct?

15 A. Yes, that's correct.

16 Q. And the skin here is called the glabella; is that
17 right?

18 A. It is.

19 Q. Skidmore did not take skin samples. They only took
20 samples that was swabbed from the patient's glabella?

21 A. What they did was the standard way of collecting skin
22 microecology specimens.

23 Q. Is that correct?

24 A. What do you mean by a skin sample?

25 Q. He didn't take -- they didn't excise any skin?

Webster - cross

1 A. They went to where the bacteria were, which was on
2 the surface, so, no, they didn't excise any skin.

3 Q. Okay. There is no bacteria located in the skin?

4 A. There is no bacteria outside or inside of the
5 epithelium. The epithelium, the outer layer is an uneven
6 thing, and there is invaginations where there is hair
7 follicles and sweat glands and such and bacteria may remain
8 seemingly in the skin but still outside the epithelium
9 because the skin goes up and down like this. But in the
10 living part of skin, there are no bacterial resident. And
11 if there are, you call it an infection.

12 Q. The skin, the follicle goes underneath the skin?

13 A. But it remains outside the skin because it is lined
14 by epithelium, the outer layer of skin.

15 Q. But Skidmore didn't sample down to the bottom of the
16 follicle, did they?

17 A. Actually, they do. The scrubbing technique takes
18 whatever is excreted from that follicle and is on the skin
19 surface.

20 Q. He did not excise anything from the follicle;
21 correct?

22 A. You don't have to.

23 Q. He didn't; right?

24 A. He didn't.

25 Q. Okay. Skidmore reported that one of his subjects in

Webster - cross

1 the Periostat group had to drop out of the study because of
2 vaginitis; is that right?

3 A. It is.

4 Q. It says, Skidmore concluded that the vaginitis was
5 considered related to Periostat treatment because of its
6 temporal relationship to administration of the study drug;
7 correct?

8 A. He said that.

9 Q. And the Skidmore study didn't have a positive control
10 either; correct?

11 A. Correct.

12 Q. Vaginitis is a side effect of doxycycline treatment;
13 correct?

14 A. Among many other things.

15 Q. You understand that the Skidmore study, like the
16 Walker 2005 study, was funded by CollaGenex?

17 A. Yes.

18 Q. You would agree with me there are hundreds of
19 bacterial genera in the body; correct?

20 A. If not millions.

21 Q. And there are many species within each bacterial
22 genera?

23 A. Yes.

24 Q. And at any given time, you understand there can be
25 millions of bacterial species present in the human body?

Webster - cross

1 A. Correct.

2 Q. Skidmore, Walker sampled a couple dozen species;
3 correct?

4 A. And species groups. So, in effect, they looked at
5 two anaerobes and two aerobes which comprises a large group
6 of organisms.

7 Q. They actually listed every single one that they
8 sampled; correct?

9 A. No, they didn't. They list the ones they identified
10 but then they also did total counts of aerobic and I think
11 facultative aerobic, if I remember the term they used.

12 Q. They did not claim to have sampled bacterial species
13 present in the body; isn't that correct?

14 MR. FLATTMANN: I think the witness was still
15 answering the question.

16 A. They claimed --

17 THE COURT: Hold on a second, doctor. There is
18 an objection. The witness was not done answering.

19 MR. FLATTMANN: The witness was not done. He
20 was answering.

21 THE COURT: It was hard to tell.

22 Now there is a question. Are you ready to
23 answer the question?

24 THE WITNESS: Would you repeat the question,
25 please.

Webster - cross

1 MR. STEUER: Okay.

2 BY MR. STEUER:

3 Q. The authors of the study did not claim to sample all
4 bacterial species present in the body; correct?

5 A. Correct.

6 Q. You would agree the serum concentration at which a
7 particular antibiotic would significantly inhibit growth
8 of bacteria varies as a function of, No. 1, the particular
9 bacterial species under examination and, No. 2, the
10 particular strains of bacteria within that species;
11 correct?

12 A. I'm not sure how No. 1 and No. 2 differ.

13 Q. Although they might not differ at all. Would you
14 agree with that?

15 A. Yes, I guess.

16 Q. Walker and Skidmore only sample bacterial populations
17 at three specific locations in the body; correct?

18 A. Correct.

19 Q. Do you agree with this statement? The assessment of
20 whether an antibiotic substance has activity against
21 microorganisms should not be limited to examining only
22 certain types of categories of bacteria?

23 A. Yes.

24 Q. And do you agree with this statement? Even if no
25 effect was observed on certain types or categories of

Webster - cross

1 bacteria associated with periodontitis, this does not
2 exclude the drugs capacity to inhibit or destroy other types
3 of microorganisms or individual bacterial strains?

4 A. What you are basically saying is does a study that
5 addresses periodontitis in the mouth address what is going
6 on in the elbow? And, you know, that is the question you
7 are asking and the answer is no. But each study within the
8 limits of what it sets out to investigate makes a statement
9 about whether there was or wasn't inhibition.

10 Q. Does that mean you agree with that statement?

11 A. With that nuance, yes.

12 Q. And -- okay. You are aware I'm reading from the FDA
13 memorandum of September 23rd, 2003, classifying Periostat as
14 an antibiotic?

15 A. I was not.

16 Q. Take a look at Defendants' Exhibit 2094.

17 Do you recognize that as the FDA memorandum on
18 Periostat?

19 A. Yes.

20 MR. STEUER: Your Honor, I would move for the
21 admission of 2094.

22 MR. FLATTMANN: No objection.

23 THE COURT: It's admitted.

24 (DTX No. 2094 received into evidence.)

25 BY MR. STEUER:

Webster - cross

1 Q. And just for your references, Dr. Webster, I was
2 quoting from page 17 of the memorandum. Do you see that
3 there?

4 A. There is two 17s. Did you say at the bottom or the
5 top of the page?

6 Q. It would be at the bottom of the page. And for the
7 record, it's about half way down the page.

8 Do you see that?

9 A. I see the page 17.

10 And what is the statement I'm looking for now?

11 Q. Okay. The assessment whether an antibiotic substance
12 has activity against microorganisms should not be limited to
13 examining only certain types or categories of bacteria.

14 A. I see that.

15 Q. Okay. Dr. Webster, you would agree the only way to
16 tell whether a drug is antibiotic in vivo against a
17 particular microorganism is to run a clinical trial of the
18 drug in the microorganism; correct?

19 A. In vivo.

20 Q. In vivo. You would agree with that?

21 A. I would agree with that.

22 Q. You do not know what the results would have been had
23 the Walker -- Skidmore and Walker researchers sampled for
24 different bacteria at different locations within a given
25 body; correct?

Webster - cross

1 A. We only know what they showed.

2 Q. We don't know one way or the other way what it would
3 have shown?

4 A. The data only speaks to the question they asked and
5 the techniques they used.

6 Q. Okay. And you cannot say whether unmeasured bacteria
7 were in fact significantly inhibited by Periostat in the
8 Skidmore and Walker studies; correct?

9 A. I can say that in bacterial rich populations like the
10 forehead, the glabella or the intestine and in other
11 Periostat studies that there was no change seen in many,
12 many, many species.

13 Q. You cannot, but we cannot say whether unmeasured
14 bacteria were significantly inhibited by Periostat in the
15 Skidmore and Walker studies; correct?

16 A. You're right. You can't address something that you
17 didn't look at or wasn't detectable.

18 Q. Okay. Doctor, would you agree that a 50-milligram
19 daily dose of doxycycline has an antibiotic effect; correct?

20 A. 50?

21 Q. Yes, 50.

22 A. Yes.

23 Q. Does 49 milligrams daily have an antibiotic effect?

24 A. It hasn't been tested.

25 Q. So you don't know one way or the other?

Webster - cross

1 A. Don't know. We have data for 50. We have data for
2 40.

3 Q. Are you aware of any studies that have compared daily
4 doses of 40 milligrams and 50 milligrams doses of
5 doxycycline for antibacterial effect?

6 A. I am not.

7 Q. Do you know of any documents, any studies that prove
8 a difference between the antibacterial effect of a 40 versus
9 50-milligram dose of doxycycline?

10 A. I'm aware of studies that show 50 milligrams rises
11 above the serum threshold of antibiotic activity but I'm not
12 aware of any studies that showed that it is suppressed
13 bacteria in vivo.

14 Q. Is 50 milligrams of doxycycline a day a therapeutic
15 dose to fight bacterium infections?

16 A. I would not use it to fight bacterium infections.

17 Q. And I think generally as you said in your direct, you
18 try to punch the infection with a sufficient dose of
19 antibiotics?

20 A. Correct.

21 Q. And that would in the normal case be more than
22 50 milligrams a day; correct?

23 A. Correct.

24 Q. You believe that a blood level of doxycycline in the
25 blood of 1.0 micrograms per milliliter is the antibiotic

Webster - cross

1 threshold; correct?

2 A. I'm not sure what the antibiotic threshold is. I'd
3 have to look.

4 Q. Okay. So you don't know if a blood level of 1.0
5 micrograms is or is not the antibiotic threshold?

6 A. I think that is probably right, but that is one of
7 those numbers that I look up.

8 Q. Have you read any studies that established that
9 antibiotic threshold?

10 A. No.

11 Q. Do you know if any studies were performed to support
12 the statement in the '267 patent that 1.0 micrograms per
13 milliliter of doxycycline is the antibiotic threshold level?

14 A. I have seen that level used, if that is what it is,
15 in several studies as the antibiotic threshold. I have not
16 seen studies that establish it.

17 Q. And you know what MIC means; correct?

18 A. I do.

19 Q. It stands for minimum inhibitory concentration;
20 correct?

21 A. Correct.

22 Q. Is it your opinion that as long as serum drug
23 concentrations of an antibiotic is below the MIC of a
24 particular microorganism, the drug will be substantially
25 without antibiotic activity against that microorganism;

Webster - cross

1 correct?

2 A. Correct.

3 Q. Now, Dr. Webster, when you were discussing
4 Dr. Feldman, you said that we don't know that the patient
5 will ever take the drug; correct?

6 A. Right.

7 Q. Do we know the patients who are prescribed Mylan ANDA
8 products will follow instructions?

9 A. In a clinical trial, there is always variance with
10 the instructions. You have a patient. But for the most
11 part, they follow the instructions because they're cajoled
12 and enhanced -- or not enhanced, but encouraged to do what
13 they're supposed to. They get phone calls. They get
14 frequent visits. Compliance is better in trials.

15 Q. Do we know patients who are prescribed Mylan's ANDA
16 product outside of a clinical trial setting will follow the
17 instructions?

18 A. I don't think anybody has been prescribed it outside
19 the clinical trial study.

20 Q. So we don't know, one way or the other?

21 A. I would assume it would be like any other drug. It's
22 not a drug that is available.

23 Q. You prescribed drugs to your patients; correct?

24 A. Correct.

25 Q. And you do that on the assumption they're going to

Webster - cross

1 administer the drugs as you prescribe; correct?

2 A. It's an assumption but a deeply flawed one.

3 Q. It's an assumption at the core of your decision to
4 prescribe medicine, isn't it?

5 A. It is. And you would think it would be an assumption
6 of the core of the patient who comes. But we know from
7 studies that compliance is sometimes 50 percent of what you
8 think it is. There are elegant studies that have patient
9 chart or patient notebooks where they record when they take
10 the drugs and when they don't. And at the same time, the
11 patient is given a bottle containing the medicine, it has a
12 computer chip in it but they're not aware until the end of
13 the study.

14 When you look at how many times the bottle has
15 been opened according to their notes, which may say
16 80 percent correct and, according to the computer chip, it's
17 almost 50 percent compliance says the computer chip. So
18 even in a study, compliances vary.

19 Q. Dr. Webster, while interesting, I'm on a clock here,
20 so I hope that you could try to confine your answers to what
21 I actually asked.

22 Dr. Webster, do we know that patients who
23 are prescribed Mylan's ANDA product will not take a
24 bisphosphonate?

25 A. We don't know that.

Webster - cross

1 Q. You talked a little bit about privacy of patient
2 records?

3 A. Yes.

4 Q. Certainly, Dr. Feldman is free to discuss the therapy
5 of naming the patient; isn't that right?

6 A. He is free to discuss the therapy without naming the
7 patient.

8 Q. In fact, it's good practice for physicians to discuss
9 therapies among themselves, isn't it?

10 A. They tend to wait until they have results.

11 Q. Is it good practice to discuss therapies?

12 A. Yes.

13 Q. And you certainly do that in your practice. Isn't
14 that right?

15 A. Yes.

16 Q. And is there any law or rule that would prevent Dr.
17 Feldman's patient from discussing the prescription for
18 Periostat?

19 A. No.

20 Q. That patient would be free to tell anyone she chose.
21 Isn't that right?

22 A. That is correct.

23 Q. Now, you stated that you do not believe that Dr.
24 Feldman anticipates in part because he didn't verify a
25 reduction in lesion counts in his patient or himself.

Webster - cross

1 Correct?

2 A. Correct.

3 Q. Are you aware that Dr. Feldman testified that his
4 rosacea went away? Correct?

5 A. Correct.

6 Q. Isn't the change in rosacea from having rosacea to
7 being absent necessarily a reduction in lesion count?

8 A. If all he is looking at is papules and pustules, yes.
9 If he is looking at other factors, no. And there is still
10 no control. Rosacea is a variable disease.

11 Q. If he says he has no rosacea, do you understand that
12 to mean he has no papules and pustules of rosacea?

13 A. Yes.

14 Q. Isn't it your expectation that if Dr. Feldman's
15 patient complied with the prescription instructions the
16 patient would have no reduction of skin microflora?

17 Correct?

18 A. If the patient took the Periostat the proper way,
19 they would have no reduction in skin microflora.

20 Q. That's what Skidmore teaches. Correct?

21 A. Correct.

22 Q. In fact, is it your opinion that the Mylan product
23 infringement is based on your assumption that patients
24 prescribed the Mylan ANDA product will follow the dosing
25 instructions? Correct?

Webster - cross

1 A. It's based on the fact that we have studies of the
2 pharmacologically identical product in the ANDA, that it had
3 the same effect as Oracea. So it is the same drug and it
4 should behave as Oracea does.

5 Q. But it will only have that effect in humans if the
6 humans take it. Correct?

7 A. Yes.

8 Q. And one assumes they will take it and that's an
9 underlying basis of your infringement opinion. Correct?

10 A. One assumes that if taken it will have certain
11 effects.

12 Q. And the assumption you make is that they will in fact
13 take it. Correct?

14 A. Yes.

15 Q. Is it your opinion that Galderma needs to count
16 lesions and take skin swabs of patients taking Mylan's ANDA
17 product in order to prove that the Mylan product infringes?

18 A. It is not my opinion that they need to do that.

19 Q. Why not?

20 A. Because that has already been done in the original
21 Oracea data and Periostat data. The FDA agreed that what
22 was done originally was sufficient for Oracea and Mylan has
23 produced a drug that is pharmacologically identical to
24 Oracea. The same drug, same effects.

25 Q. So your opinion today is that we know that a patient

Webster - cross

1 that takes this preparation will have a reduction in lesions
2 and no reduction -- no reduction in skin microflora?

3 A. That is my opinion.

4 Q. Dr. Webster, you testified that prior to the Ashley
5 patents it was believed that the Helicobacter species was
6 thought of as a cause of rosacea. Correct?

7 A. Correct.

8 Q. However, that theory was disapproved prior to the
9 Ashley patents. Correct?

10 A. I don't think that's true.

11 Q. Didn't you report that yourself?

12 A. I reported that there was conflicting data. But it
13 was still widely held, and still to this day is believed by
14 many.

15 Q. Conflicting data?

16 A. There were data, papers, perhaps. I don't have
17 anything in front of me that you are talking about, that may
18 have said that, well, maybe it's not involved. But the
19 weight of the data at the time said that it was.

20 Q. Now I would like to get to Exhibit 2323, which I
21 handed up earlier: It's an article entitled Acne Vulgaris
22 and Rosacea, Evaluating and Management, by Guy F. Webster.
23 It's 2323. Is this an article you wrote?

24 A. It is.

25 MR. STEUER: I offer it.

Webster - cross

1 MR. FLATTMANN: No objection.

2 THE COURT: It's admitted.

3 (Defendants' Trial Exhibit No. 2323 received in
4 evidence.)

5 BY MR. STEUER:

6 Q. Let me call your attention to, I guess it's the fifth
7 page of the article, it's on Page 19.

8 Incidentally, do you recall what year this was
9 published?

10 A. I have no idea.

11 Q. Does 2001 sound right?

12 A. I don't know. Could be.

13 Q. And there is a discussion here of rosacea. If you
14 look at the second paragraph there, if you look at the last
15 sentence of that second paragraph, it says, the last
16 sentence, gastric disease caused by Helibactora species was
17 once complicated but now has been disproved as a cause of
18 rosacea. Do you see that?

19 A. I do.

20 Q. That's what you wrote in this article?

21 A. That's what I wrote.

22 Q. And in the next paragraph, that starts Topical Drugs,
23 the second sentence says, Ocular rosacea and more severe
24 inflammatory rosacea respond well to oral doxycycline. Do
25 you see that?

Webster - cross

1 A. Yes.

2 Q. And this is ocular rosacea, meibomian gland disease
3 is a form of ocular rosacea?

4 A. That is part of it, yes.

5 Q. This is an ailment that you discuss here in your
6 discussion of rosacea. Is that right?

7 A. Yes.

8 Q. Now, you testified that prior to the Ashley patents,
9 the prior art taught that antibiotic effects are needed to
10 treat acne. Correct?

11 A. Yes.

12 Q. But, in fact, that's not the case, is it?

13 A. No. Acne still requires antibiotic effects to get
14 significant improvement. There are studies showing that
15 lower dose gets some improvement. But it is not a
16 satisfactory response rate.

17 Q. In fact, it's been known for many years that a
18 non-bacteriostatic concentration could be useful in acne.
19 Isn't that right?

20 A. I don't think that's true.

21 Q. All right. Let me ask you to turn to Defendants'
22 Trial Exhibit 1840. Do you have the Plewig article in front
23 of you?

24 A. I do.

25 Q. This is an article called Acne: Morphogenesis and

Webster - cross

1 Treatment.

2 Do you see that?

3 A. Yes.

4 Q. From 1975?

5 A. Yes.

6 Q. Okay. And you are familiar with this study.

7 Correct?

8 A. I am familiar -- this is not a study --

9 Q. A summary?

10 A. Yes.

11 Q. But you are familiar with it. Right?

12 A. Yes.

13 MR. STEUER: I offer Defendants' Trial Exhibit

14 1840.

15 MR. FLATTMANN: No objection.

16 THE COURT: It is admitted.

17 (Defendants' Trial Exhibit No. 1840 received in
18 evidence.)

19 BY MR. STEUER:

20 Q. Let me ask you to turn to Page 300. That would be
21 MYL D098333. There is a sentence that starts at the bottom
22 of the first column, it says, "We have shown that both
23 fluorescence and free fatty acid can be greatly reduced even
24 when there is no change in the density of C.acne. The
25 antibiotic can affect the metabolic activities and inhibit

Webster - cross

1 the production of injurious products at non-bacteriostatic
2 concentrations.

3 Do you see that?

4 A. I see that.

5 Q. This is what Plewig wrote in 1975?

6 A. Yes.

7 Q. In general, that is the theory of the Ashley patents
8 25 years later, is it not?

9 A. It is not. The Ashley patents talk about the growth
10 of bacteria being suppressed. They specifically say here
11 that there is no change in the growth, in the populations of
12 the acnes. I actually did a publication a few years after
13 this --

14 Q. Dr. Webster, I didn't ask you about your
15 publications.

16 MR. FLATTMANN: Objection, Your Honor.

17 THE COURT: Let's allow the witness to continue
18 his answer.

19 THE WITNESS: -- trying to investigate why the
20 free fatty acids in skin go down before C acne cells go
21 down. We looked at whether antibiotics can change the
22 enzyme the C acne uses to make the free fatty acids. And it
23 showed it clearly inhibited its production without affecting
24 in the least the growth of the C acne. And it was published
25 somewhere back in the late seventies or early eighties.

Webster - cross

1 MR. STEUER: Nothing further.

2 THE COURT: Any redirect?

3 MR. FLATTMANN: Just some short redirect, Your
4 Honor.

5 REDIRECT EXAMINATION

6 BY MR. FLATTMANN:

7 Q. You were asked, Dr. Webster, about consulting for
8 CollaGenex and Galderma. Do you recall that?

9 A. Yes.

10 Q. Do you consult for other pharmaceutical companies?

11 A. I consult with just about everyone with a product for
12 acne.

13 Q. Can you name some of the companies you would consult
14 for?

15 A. Allergan, GlaxoSmithKline, Galderma, Allocore.

16 Q. In your opinion, why are you called on to consult for
17 these companies?

18 A. Actually, acne is kind of an academic back water.

19 There is not many people who have been around long enough to
20 acquire the knowledge that these guys need.

21 Q. You were asked some questions about the Skidmore and
22 Walker studies. Do you recall that?

23 A. Yes.

24 Q. And how does the fact that the Skidmore and Walker
25 studies did not investigate every single bacteria or every

Webster - redirect

1 body cavity affect your opinions in this case?

2 A. It doesn't change my opinions. Studies only can be
3 judged on what they show. You can't expect one study to be
4 authoritative. But the evidence that we have is that
5 bacteria under the influence of this amount of doxycycline
6 don't change.

7 Q. What do these studies tell you about reduction of
8 skin microflora?

9 A. None of them have shown reduction of skin microflora.

10 Q. How do you know that?

11 A. Because they studied it and they didn't find it.

12 Q. You were asked some questions about a 50-milligram
13 once-a-day dose of doxycycline. Do you recall that?

14 A. Yes.

15 Q. And is it your view that an antibacterial amount or a
16 sub-antibacterial amount?

17 A. It reaches levels that are antibacterial.

18 Q. And he directed you to some references and some
19 papers that you were a named author on, where he quoted you
20 as writing that doxycycline was used to treat acne in
21 dosages of 50 to a hundred milligrams QD to BID. Do you
22 recall that?

23 A. I do.

24 Q. In your opinion, was 50 milligrams of doxycycline QD
25 a commonly used dosage to treat acne or rosacea in 2000?

Webster - redirect

1 A. It was not.

2 Q. What doses were typical at that time?

3 A. A hundred or 200.

4 Q. And what is your understanding of the meaning of the
5 reference in those articles to dosages of 50 to a hundred
6 milligram QD to BID?

7 A. Those are the available dosages at the time and at
8 least in one paper it was inserted by the editors.

9 Q. In your view, why was it that doctors did not
10 commonly use a dosage of 50 milligrams of doxycycline to
11 treat rosacea?

12 A. Because they didn't think it would work.

13 Q. As of 2000, in your view, would the availability of
14 50 milligrams of doxycycline QD have rendered obvious the
15 use of sub-antibacterial doses of doxycycline to treat
16 rosacea?

17 A. It would not have rendered it obvious because it's
18 still in the antimicrobial range.

19 Q. You were asked a couple of questions about the one
20 microgram per ml threshold. Do you recall that?

21 A. I do.

22 Q. And to what degree do you rely on that one microgram
23 per ml threshold in forming your opinions that the Mylan
24 products infringe?

25 A. That is the threshold that has been cited in the

1 literature. It's been approved by reviewers and is
2 accepted.

3 Q. What evidence do you rely on to show that the Mylan
4 products do not significantly inhibit growth?

5 A. Well, we have data showing that they don't inhibit
6 the growth of bacteria.

7 Q. What data are you referring to?

8 A. The Walker and the Skidmore papers.

9 MR. FLATTMANN: No further questions, Your
10 Honor.

11 THE COURT: Okay. Thank you. You may step
12 down, Dr. Webster.

13 (Witness excused.)

14 THE COURT: Call your next witness.

15 MS. WILLGOOS: Your Honor, plaintiffs would like
16 to call Dr. Rudnic.

17 THE COURT: Okay.

18 ... EDWARD MICHAEL RUDNIC, having been duly
19 sworn as a witness, was examined and testified as
20 follows ...

21 THE COURT: Good afternoon, Dr. Rudnic.

22 DIRECT EXAMINATION

23 BY MS. WILLGOOS:

24 Q. Good afternoon.

25 MS. WILLGOOS: May I hand up witness binders and

Rudnic - direct

1 slides, please?

2 THE COURT: You may do so. Why don't you take a
3 moment to remove the stuff from Dr. Webster. Thank you.

4 BY MS. WILLGOOS:

5 Q. Dr. Rudnic, could you please state your name for the
6 record?

7 A. My name is Edward Michael Rudnic.

8 Q. Where are you currently employed?

9 A. I am self-employed as a consultant and venture
10 capitalist.

11 Q. What field do you consult in?

12 A. Formulation development, controlled release products,
13 pharmaceutical development, and pharmaceutical business in
14 general.

15 Q. Can you briefly describe your educational background
16 for the Court?

17 A. I have a Bachelor's in pharmacy, and am a registered
18 pharmacist. I have a Master's in pharmaceutics and a Ph.D.
19 in pharmaceutical sciences, all from the University of Rhode
20 Island.

21 Q. When did you obtain your Ph.D.?

22 A. 1982.

23 Q. And can you describe your professional background?

24 A. My professional background, including my graduate
25 work and working post-graduate was with some very large

Rudnic - direct

1 pharmaceutical companies, Merck, Lederle, Schering-Plough,
2 Squibb, which is now Bristol-Myers Squibb, and then some
3 smaller companies all involved with the formulation and
4 development of controlled release products, novel drug
5 delivery systems and pharmaceutical products in general,
6 culminating with me being the CEO of an antibiotic company
7 that I took public in 2003.

8 Q. Do you hold any academic positions?

9 A. I have two. I am an adjunct professor at the
10 University of Maryland in Baltimore. And I am an adjunct
11 professor at the University of Rhode Island.

12 Q. Have you ever published in any scientific literature?

13 A. I have over 20 articles that have appeared in
14 peer-reviewed journals. And I have published seven textbook
15 chapters in textbooks such as Modern Pharmaceutics and
16 Remington's Pharmaceutical Sciences.

17 Q. What is the subject matter of those publications?

18 A. Those are all formulation development, oral
19 controlled release, oral solid dosage form development.

20 Q. Are you involved in any professional organizations
21 relating to pharmaceuticals?

22 A. Several. I am very active in the American Society of
23 Pharmaceutical Scientists, ASPS, and the Technology Council
24 of Maryland, and MDBio, which is a subset of the
25 biotechnology industry organization.

Rudnic - direct

1 Q. How many of the drugs that you have worked on during
2 your career have been commercialized?

3 A. Over 80 products that I have worked on personally
4 have been commercialized. About five of which I was
5 personally involved as either the lead inventor or
6 co-inventor have been commercialized.

7 Q. Collectively, how much money in annual sales or
8 collective sales have those drugs earned as far as you are
9 aware?

10 A. Well over a hundred billion dollars.

11 Q. Dr. Rudnic, can you please turn in your binder to the
12 tab that has been marked as PTX-247?

13 THE COURT: Ms. Willgoos, could you pull the
14 microphone a little closer to you.

15 MS. WILLGOOS: I am sorry, Your Honor.

16 THE COURT: Thank you.

17 BY MS. WILLGOOS:

18 Q. Do you recognize this document?

19 A. I do.

20 Q. What is this?

21 A. This is a copy of my resume, as well as the patent
22 record.

23 Q. Does it fairly and accurately summarize your
24 educational and professional experience?

25 A. It does.

Rudnic - direct

1 MS. WILLGOOS: Your Honor, Galderma would like
2 to submit PTX-247 into evidence.

3 MR. STEUER: No objection.

4 THE COURT: Received.

5 (Plaintiffs' Trial Exhibit No. 247 received in
6 evidence.)

7 MS. WILLGOOS: We would also like to tender Dr.
8 Rudnic as an expert in the field of pharmaceutical drug
9 development and formulation.

10 MR. STEUER: No objection.

11 THE COURT: He is so recognized.

12 BY MS. WILLGOOS:

13 Q. Dr. Rudnic, I know you have demonstratives with you.
14 Can you tell us how these slides were prepared?

15 A. I prepared them with the assistance of counsel.

16 Q. Can you please turn to your exhibit binder, PTX-5.
17 What is this document?

18 A. This is the Chang patent, as it's been called earlier
19 today, or the '532 patent.

20 Q. Have you reviewed this patent in forming your
21 opinions in this case?

22 A. I have.

23 MS. WILLGOOS: Your Honor, Galderma would like
24 to submit PTX-5 into evidence.

25 MR. STEUER: No objection.

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1 THE COURT: Its it is admitted.

2 (Plaintiffs' Trial Exhibit No. 5 received in
3 evidence.)

4 BY MS. WILLGOOS:

5 Q. Let's turn to your first slide, 201. Can you
6 describe for us what the subject matter of the Chang patent
7 is?

8 A. The Chang patent is quite simply a once-daily
9 formulation of doxycycline. And it's a controlled release
10 product that comprises 30 milligrams of an immediate release
11 dosage and 10 milligrams of an enteric coated delayed
12 release dosage. It's designed to meet very specific and
13 certain steady state blood levels.

14 Q. Are any methods described in the Chang patent?

15 A. There is a method of treating rosacea.

16 Q. Have you formed any opinions regarding the Chang
17 patent?

18 A. I have.

19 Q. Let's turn to your next slide. Dr. Rudnic, can you
20 summarize for us your opinions regarding infringement of the
21 Chang patent?

22 A. I believe Mylan's generic version of Oracea infringes
23 the Chang patent.

24 Q. Have you formed any opinions regarding validity?

25 A. I have.

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1 Q. What are your opinions regarding validity?

2 A. I believe the Chang patent is valid and I don't
3 believe it's obvious and I don't believe it's anticipated.

4 Q. And what materials have you relied on in connection
5 with your opinions?

6 A. Well, I have looked at the Chang patent, obviously.
7 I have also looked at Mylan's development report, which is
8 part of their ANDA, it's called the quality report or
9 development report, part of their ANDA, as well as their
10 product labeling.

11 Q. Before we get to your opinions, I'd like to discuss
12 some background information so the Court and everyone in the
13 courtroom is aware of the science.

14 Let's turn to your next slide.

15 Can you describe for us what an immediate
16 release drug formulation is?

17 A. Well, immediate release is something that is -- that
18 liberates the drug promptly upon administration.

19 Q. What is a controlled release drug formulation?

20 A. A controlled release is one that deliberately and in
21 some manner holds back on the release of drug in some
22 controlled manner.

23 Q. Okay. What about a delayed release drug formulation?

24 A. A delayed release in general has no drug release
25 after ingestion of the dosage form and then it is targeted

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1 to a certain area of the GI tract or a particular time after
2 ingestion and then release occurs.

3 Q. And what about a sustained release drug formulation?

4 A. Sustained release is a lot like controlled release
5 but it is more a slow release or a very defined slow
6 liberation of the drug so that it is absorbed slowly into
7 the body.

8 Q. And which of these types of formulations, if any,
9 could be used to formulate a once-a-day product?

10 A. All of them can. In fact, I have used all of these
11 technologies to develop once-a-day products.

12 Q. And how could you determine or how could one of skill
13 in the art determine which appropriate -- which formulation
14 is appropriate for a particular drug?

15 A. Well, it would depend on the drug. It depends on
16 its physical characteristics, a lot of the absorption
17 characteristics of the drug, and the goal of the project
18 that you are attempting to accomplish as to whether or not
19 it's a once-a-day, but you can use all of these. And also
20 how you engineer these technologies is a big factor.

21 Q. Let's discuss some basics about pharmacokinetics. We
22 can go to the next slide.

23 But first, can you tell us what is
24 pharmacokinetics.

25 A. Pharmacokinetics is simply the drug or its

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1 metabolites in a body fluid.

2 Q. What is a single dose plasma profile as you set it
3 out in this slide?

4 A. Well, plasma is a component of blood, and this is a
5 one-off administration of a dose. So what you have is the
6 rise and fall of the drug concentration as the drug is
7 absorbed and then eliminated and that is the plasma time
8 curve that we see.

9 Q. Okay. And what is the definition of area under the
10 curve?

11 A. Area under the curve is the geometric area under that
12 plasma time curve, and it represents the total amount of
13 drug absorbed by that dose.

14 Q. What is the Cmax?

15 A. The Cmax is the maximum concentration achieved in
16 that plasma time curve, and it is also known as the peak.

17 Q. Okay. And what about Tmax? What is the definition
18 of that term?

19 A. The Tmax is simply the time at which the Cmax is
20 observed.

21 Q. Let's turn to your next slide, 205.

22 What is steady state?

23 A. Well, steady state is where you have multiple doses
24 that are given to where ultimately your plasma time curve is
25 quite consistent from one dose to the next. And what I have

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1 highlighted here in this particular case, the plasma time
2 curve in that third dose is equivalent to the one before it
3 and the one after it. And that is a good indication that
4 you are at steady state.

5 Q. What is the Cmin or trough as you have set it out in
6 this graph?

7 A. Well, Cmin is the minimum concentration in that
8 multiple dose plasma time curve, and sometimes it's called
9 the trough. So peak and trough are Cmin and Cmax.

10 Q. Let's next discuss your opinions regarding
11 infringement and we can turn to slide 206.

12 Does Mylan infringe the Chang patent?

13 A. Well, I think we have all heard that Mylan admits
14 infringement of most of the claims. But in my view, they
15 also infringe claims 4 and 18.

16 Q. Okay. And let's turn to our next slide. What is the
17 formulation of Mylan's generic product?

18 A. Well, Mylan's generic product is an oral capsule
19 which contains 40 milligrams of doxycycline. It also has
20 30 milligrams immediate release beads and 10-milligram
21 enteric coated delayed release beads, and it has
22 pharmaceutical excipients such as triethyl citrate and talc.

23 Q. What is the label indication of Mylan's generic
24 product?

25 A. It's indicated for inflammatory lesions of rosacea.

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1 Q. And what materials have you relied on in connection
2 with your infringement opinions?

3 A. Well, I have looked at their development report,
4 "their" meaning Mylan's development report for their generic
5 product, the Chang patent, and the labeling that Mylan has
6 for their product.

7 Q. Let's turn in your exhibit binder to DTX-2267.

8 A. Yes.

9 Q. What is that document?

10 A. That is what they call quality overall summary. It
11 is known in the term of the art as a development report that
12 is really development of the formulation for their ANDA.

13 MS. WILGOOS: Your Honor, Galderma would like to
14 move into evidence DTX-2267.

15 MR. STEUER: No objection.

16 THE COURT: It's admitted.

17 MS. WILGOOS: Thank you.

18 BY MS. WILGOOS:

19 Q. Let's turn to slide 208.

20 What have you set forth for us here?

21 A. Well, here are claims 4 and 18. And I highlight them
22 because they're dependent claims and they're dependent on
23 claims 1 and 15, respectively.

24 Q. And what are the sections of these claims that you
25 have highlighted for us?

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1 A. Well, what we have is in claim 4, which is the
2 independent claim, a steady state blood level of doxycycline
3 of a minimum of .1 to a maximum of 1 microgram per mil and
4 claim 4 depends on that and refines it 0.3 to 0.8 micrograms
5 per mil, and similarly claim 15 and claim 18 do the same
6 thing.

7 Q. Okay. Have you formed an opinion regarding whether
8 Mylan's generic product meets the claim limitations that are
9 highlighted on this slide?

10 A. I have.

11 Q. And what is your opinion?

12 A. That they infringe claims 4 and 18.

13 Q. Okay. What materials have you relied on in forming
14 your opinions?

15 A. I have relied on the pivotal pharmacokinetic study.

16 Q. Can you please turn in your exhibit binder to
17 PTX-464?

18 A. Yes.

19 Q. And what is this document?

20 A. This is a clinical study report by Covance that was
21 sponsored by CollaGenex.

22 Q. So CollaGenex sponsored the study; correct?

23 A. That's correct.

24 Q. How is it that you rely on it for your opinions
25 regarding infringement of Mylan's product?

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1 A. Well, because the claims are for steady state and
2 Mylan has no data for steady state blood levels, but what
3 they do have is a single dose bioavailability study both in
4 the fed and fasting state.

5 Now, these are very vigorous and discriminating
6 bio studies. So when you have an extended release product,
7 when you have both the fed and fasting in a single dose that
8 are met, you will meet substantially the steady state blood
9 levels for that product that you have just matched, and the
10 FDA agrees with that, which is why they require those two
11 types of studies.

12 MS. WILGOOS: Your Honor, plaintiff would like
13 to move PTX-464 into evidence.

14 MR. STEUER: No objection.

15 THE COURT: It's admitted.

16 (PTX No. 464 received into evidence.)

17 BY MS. WILGOOS:

18 Q. Now, Dr. Rudnic, have you formed an opinion regarding
19 whether Mylan's generic product meets the specific claim
20 limitation of a minimum of .1 to a maximum of 1.0 micrograms
21 per milliliter?

22 A. I have.

23 Q. Can we turn to the next slide, 209, please?

24 What have you set us for us on this slide?

25 A. I know it's hard to read but, visually, what this is

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1 are the plasma levels for 31 normal volunteers in the
2 pivotal pharmacokinetic study that we just spoke about.

3 Q. Okay. And how does that inform your opinion
4 regarding the claim limitation of blood levels of a minimum
5 of .1 to a maximum of 1.0 micrograms per milliliter?

6 A. Well, 30 of the 31 subjects here all meet that
7 limitation.

8 Q. Okay. What about the claim limitation of having
9 blood levels between 0.3 micrograms per milliliter to
10 0.8 micrograms per milliliter?

11 A. Well, there are three subjects in particular that
12 meet that at all time points, and the majority of those
13 subjects meet them at the vast majority of those time
14 points, and those are highlighted in green just for visual
15 effect.

16 Q. Sure. So just for clarification, you said those are
17 highlighted in green. You believe the patients in green
18 meet the claim limitation of 0.3 to 0.8 micrograms per
19 milliliter; is that correct?

20 A. That's correct.

21 Q. Now, I noticed you have a key set forth on the side
22 of this, nanograms to micrograms. Can you explain that for
23 us?

24 A. Well, the measurements here were in nanograms per
25 mil, which are one thousandth of a microgram per mil, so in

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1 order to kind of convert these into the same measurements
2 that are listed in the patent, you would have to divide
3 these by a thousand.

4 Q. After reviewing the data, have you formed an opinion
5 regarding whether a person of ordinary skill in the art
6 would understand from reading the Chang patent that the
7 Chang inventors actually invented a formulation that will
8 give steady state blood levels of between 0.3 to
9 0.8 micrograms per milliliter?

10 A. Yes, I have; and I believe they did.

11 Q. And what is your opinion based on?

12 A. Based on the study.

13 Q. Let's turn to our next slide. 210.

14 Dr. Rudnic, have you also formed an opinion
15 whether Oracea, Galderma's product, is covered by the claims
16 of the Chang patent?

17 A. I have.

18 Q. Okay. And what is your opinion?

19 A. My opinion is that Oracea is covered by the Chang
20 patent.

21 Q. Okay. And what is the Oracea formulation?

22 A. Well, Oracea is an oral capsule, and it contains
23 40 milligrams doxycycline. It has 30 milligrams immediate
24 release beads, it has 10 milligrams enteric coated delayed
25 release bead, and its has pharmaceutical excipients,

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1 triethyl citrate, and others.

2 Q. Have you considered the steady state blood levels of
3 Oracea in forming your opinion?

4 A. I have.

5 Q. Okay. And what is your opinion regarding whether
6 those blood levels meets the claim limitations of the Chang
7 patent?

8 A. I believe the steady state blood levels that we just
9 looked at meet those claims in the Chang patent.

10 Q. And what is Oracea indicated for?

11 A. It's indicated for the inflammatory lesions of
12 rosacea.

13 Q. Okay. Let's turn to your opinions regarding
14 validity. And let's turn to our next slide.

15 Have you reviewed the art that is cited by
16 Mylan's expert, Dr. Friend?

17 A. I have.

18 Q. And what is your opinion regarding that art?

19 A. Well, I believe that none of that art really reads
20 upon the invention of the Chang.

21 Q. Okay. Let's discuss some background information. I
22 think we need to understand the invention.

23 And we can turn to your next slide, 212.

24 What is an absorption window?

25 A. Well, an absorption window is one where you would

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1 have normally high or acceptable absorption in one area of
2 the gastrointestinal tract followed by abnormally low or not
3 appropriate or not acceptable levels of drug absorption in
4 other parts of the gastrointestinal tract. So it is said to
5 have a window of absorption for that particular drug.

6 Q. And how is that depicted on this slide?

7 A. Well, here, what we show is that, for a typical
8 product that might be released in the stomach, which is the
9 upper part of where that red is, it would then go into
10 solution and the drug would then go through the valve of the
11 stomach called the pylorus into the duodenum. And where I
12 show red, you have absorption of the drug in the upper part
13 of the GI tract.

14 The blue portion is where you start to have less
15 absorption or no absorption of the drug.

16 Q. And does an absorption window matter to a drug
17 formulator?

18 A. It's critical. If you don't know that you have an
19 absorption window, you are likely to fail your first
20 attempts extended release dosage form and not know why.

21 If you know that you have an absorption window,
22 it's quite important that you release all of the drug either
23 before or during that window so that it's available for
24 absorption. If you release it afterwards, it's not
25 absorbed.

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1 For doxycycline, that is especially problematic
2 because if you have unabsorbed antibiotics even at a very
3 low concentration, it can have a very high concentration in
4 the lumen of the gut, in the intestinal tract, and so it can
5 have a very bad effect on the bacteria that are in the GI
6 tract. So that would be bad for doxycycline.

7 Q. So just to clarify, does doxycycline have an
8 absorption window?

9 A. It does.

10 Q. Let's turn to your next slide, 213.

11 What, if anything, was known about the
12 absorption window of doxycycline in the 2002-2003 time
13 frame?

14 A. Well, an absorption window was not known. In fact,
15 it's not even well known today. I have searched quite
16 recently at the National Library of Medicine and you don't
17 see anything on an absorption window on doxycycline. But
18 back in 2002 and 2003, I looked at the primary literature, I
19 looked at textbooks from that point in time, and all that we
20 can find out was that the immediate release form was well
21 absorbed in the duodenum, but there is no teachings
22 regarding what the absorption is in the jejunum, the ileum,
23 or the colon. So other portions of the GI tract are largely
24 silent.

25 Q. So what conclusions have you reached regarding

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1 whether a person of ordinary skill in 2002 or 2003 would
2 have known about the absorption window of doxycycline?

3 A. A person of ordinary skill in that time frame, or
4 even today, searching would not know that there is an
5 absorption window. In fact, they would probably see that
6 there is a green light for very good absorption primarily in
7 the duodenum.

8 Q. Can you please turn in your exhibit binder to
9 PTX-504.

10 A. Yes.

11 Q. What is this document?

12 A. This is the protocol from CollaGenex for a very
13 specialized bioavailability study on the absorption of
14 doxycycline.

15 Q. What is the date of that report?

16 A. June 6th, 2002.

17 Q. Can you turn to PTX-469 in your exhibit binder?

18 A. Yes.

19 Q. What is this document?

20 A. This is the study report from Scinta Pharma. It's a
21 very, very specialized study using gamma radiation to track
22 the remote control capsule that is released remotely into
23 various parts of the GI tract when tracking an individual
24 patient.

25 Q. What is the date of that report?

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1 A. This is, February 10th, 2003 is the final study
2 report.

3 Q. Did you review these two documents, PTX-504 and
4 PTX-469, in forming your opinions?

5 A. I have.

6 MS. WILGOOS: Your Honor, at the time, Galderma
7 would like to move PTX-504 and 469 into evidence.

8 MR. STEUER: No objection.

9 THE COURT: They're admitted.

10 (PTX No. 469, 504 received into evidence.)

11 BY MS. WILGOOS:

12 Q. Let's turn to the next slide.

13 Now, can you just very briefly for us describe
14 the studies that were conducted.

15 A. In early 2000, as we saw, CollaGenex commissioned the
16 study of absorption of doxycycline. And as I said before,
17 this is a really neat, very specialized technology. They
18 have, they use gamma scintigraphy, which is to say they used
19 a radioactive substance to track the remote controlled
20 capsule as it passes through the GI tract, and when it hits
21 a specific region of the intestine that they want to release
22 the drug, they can hit a button, it opens a trap door and
23 the powder of doxycycline is released in that particular
24 area.

25 Q. What was the conclusion of this study?

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1 A. Well, it showed that there was an absorption window.
2 That high up in the GI tract, up in the duodenum, you had
3 almost perfect absorption. And about a little less than
4 half of that, in the later parts of the small intestine, the
5 jejunum and ileum, and almost nothing in the colon.

6 Q. Are you aware of whether or not the study was
7 publicly available?

8 A. It's not publicly available, and I can't find it when
9 I search for it today.

10 Q. Okay. Thank you. Let's talk specifically about your
11 invalidity opinions and the references that Dr. Friend
12 relies on.

13 Let's turn to your next slide, 215.

14 And what have you set out for us here,
15 Dr. Rudnic?

16 A. Well, Dr. Friend throws a lot of references at us and
17 for me to consider, and so what I have done is I have
18 grouped them into seven different categories just for ease
19 of discussion.

20 Q. Okay. And what is the relevance of these references
21 to the formulation of a once daily doxycycline product that
22 does not have antibiotic effect?

23 A. I don't believe any of them have any relevance.

24 Q. Let's talk about them one at a time. If you could
25 turn to slide 216.

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1 What are the Ashley patent applications?

2 A. Well, these are all from the same patent family.

3 They were talked about earlier but it's the '854
4 application, the '106 application and the '261 publication.

5 Q. Okay. And did you review each of these references in
6 connection with your opinions in this case?

7 A. I did.

8 Q. And what generally is the subject matter of these
9 patent applications?

10 A. Well, they talked about the general idea of a once
11 daily administration, but there is no examples of any
12 formulations that were actually made. This is really a
13 concept paper.

14 Q. Okay. And do you have an opinion regarding whether
15 these Ashley patent applications anticipate the invention of
16 the Chang patent?

17 A. I believe they don't.

18 Q. Let's turn to your next slide. If you could explain
19 for us the basis of your opinion?

20 A. Well, if you look at those three documents, all
21 throughout those documents the word substantially constant
22 rate is used, actually all the way through all three
23 documents. What he is trying to do is have a constant
24 steady rate for a slow release, if you will, of 12 to 24
25 hours, as the preferred embodiment of what he is trying to

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1 accomplish here.

2 This is not an immediate release/delayed release
3 kind of thing that happens. In Chang's release, it happens
4 well earlier than six hours.

5 So all the release that is happening with these
6 Ashley patent applications teaches away, they are teaching a
7 sustained release, a controlled release type product in a 12
8 to 24-hour time period.

9 Q. Do you understand that Mylan's expert, Dr. Friend,
10 opines that these patent applications teach the use of IR/DR
11 formulation?

12 A. I understand that. But I couldn't disagree more.

13 Q. Let's turn to your next slide, Slide 218. Can you
14 explain the basis for your disagreement with Dr. Friend?

15 A. Well, on top of the fact that Ashley continually,
16 constantly is talking about a constant release, he explains
17 his main exhibit for this in that he has three different
18 components, but all three release agents are in there, and
19 he relies mostly, in this figure, on the sustained release,
20 to carry most of that release over that 12 to 24-hour
21 period.

22 I would also like to point out that the delayed
23 release that he has doesn't start to release until 12 hours.
24 And because of the absorption window with doxycycline, that
25 would be virtually no doxycycline would be absorbed from

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1 this dosage form.

2 Q. Okay. Let's look at a portion of one of these, the
3 '106 application that Dr. Friend relies on. If we could
4 turn to Slide 219, please?

5 Now, in your opinion, Dr. Rudnic, what type of
6 formulation is taught in this portion of the patent
7 specification?

8 A. Well, in this portion of the patent, Ashley is
9 talking about a gastro-retentive formulation. If you see
10 the highlighted words up there, entrapped in the upper
11 portion of the gastrointestinal tract. The only way to do
12 that is to keep it from crossing the pylorus. Ashley
13 suggests we can do that by having a large particle size of
14 the tablet or pellet or whatever we are doing, and that, in
15 fact, would be a gastro-retentive system.

16 Q. If we can turn to your next slide. If you could just
17 very briefly describe for us what a gastro-retentive system
18 is?

19 A. In here, you see, in the top left chart, you see a
20 tablet being swallowed and going to the stomach. In the top
21 right chart you see that the tablet is starting to release
22 drug. And I have the tablet in blue and the drug that is
23 being released in the solution in pink. And then on the
24 bottom chart, you can see that the tablet stays in the
25 stomach, but the drug that is in solution is leaking out of

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1 the pylorus into the intestinal tract and being absorbed.

2 Q. And how does that compare with an IR/DR formulation?

3 A. Night and day. If you know you have an absorption
4 window, you probably would want to go towards a
5 gastro-retentive system. You would probably want to stay
6 away from an IR/DR system.

7 Q. Let's turn to Dr. Friend's next group of references
8 in your next slide. What are the Ashley patent
9 applications -- I am sorry, the Ashley method-of-use
10 patents? I apologize.

11 THE COURT: Before we get into that, I think we
12 ought to take our lunch break.

13 We will be in recess until 1:45.

14 (Luncheon recess taken.)

15 THE COURT: You may proceed with your
16 examination.

17 BY MS. WILLGOOS:

18 Q. If we could proceed with Slide 221, which is where we
19 left off.

20 Can you just summarize for us your opinions
21 regarding whether the Ashley patent applications that we
22 were discussing before the break anticipate or render
23 obvious the inventions of the Chang patent?

24 A. These patent applications don't disclose, they don't
25 teach, they don't even have such a formulation of the Chang

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1 patent. They don't mention a 30 milligram IR, ten milligram
2 DR or doxycycline. And they don't mention anything about
3 treating rosacea.

4 Q. Let's turn to the next group of references, the
5 Ashley method-of-use patents, then we can advance to Slide
6 222. What are the Ashley method-of-use patents?

7 A. This is a family of patents and applications that are
8 issued.

9 This is the Ashley '267 patent, the Ashley '572
10 patent, and the '932 application.

11 Q. Have you reviewed these three applications in forming
12 your opinions?

13 A. I have.

14 Q. Can you generally describe for me what this group of
15 references relates to?

16 A. They relate directly to the use of sub-antimicrobial
17 doxycycline in treating acne and rosacea. By the way, there
18 is no formulation patents at all in these documents.

19 Q. Do you have an opinion regarding whether the Ashley
20 method-of-use patents anticipate or render obvious the
21 inventions of the Chang patent?

22 A. I do. I believe they do not.

23 Q. Let's advance to your next slide. Can you please
24 tell us the basis of your opinion?

25 A. Well, they don't disclose, they don't teach, and they

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1 don't each suggest a formulation of the Chang patent. They
2 don't have an actual once-daily formulation. And the 30
3 milligram IR portion or ten milligram DR portion is not even
4 contemplated or disclosed.

5 Q. Thank you. If we could please turn to your next
6 slide and Dr. Friend's next group of references. What are
7 the amphetamine patents?

8 A. The amphetamine patents are the Burnside '819 patent,
9 which I know very well since I am a co-inventor on that
10 patent, and Couch '768 patent. These are basically patents
11 that are directed towards a product called Adderall XR.

12 Q. Did you review both of these patents in forming your
13 opinions in this case?

14 A. I have.

15 Q. And how do the amphetamine patents relate to
16 formulations of doxycycline?

17 A. They don't.

18 Q. Can you explain the basis for your opinion?

19 A. Well, amphetamines are completely different drugs.
20 They are very, very water soluble, whereas doxycycline is
21 not nearly that.

22 So they are absorbed all throughout the GI
23 tract, almost perfectly so. And they require, in order for
24 the amphetamines to work, specifically in the attention
25 deficit, which is the purpose of these patents, it requires

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1 a continually increasing plasma concentration to keep the
2 receptors turned on.

3 The last thing you would want there is a flat,
4 steady plateau.

5 Whereas with doxycycline, instead of very good
6 absorption, you have an absorption window. And it requires
7 dosing under a certain plasma concentration level. In other
8 words, they want a very steady, low level for a therapeutic
9 effect. Completely opposite in terms of their approach and
10 objectives.

11 Q. Have you formed an opinion regarding whether the
12 amphetamine patents anticipate or render obvious the
13 inventions of the Chang patent?

14 A. I have, and they do not.

15 Q. Let's turn to your next slide, 224. Can you explain
16 for us the basis for your opinion that they don't anticipate
17 or render obvious the Chang patent?

18 A. Well, as I said before, I mean, you know, those
19 patents don't talk about doxycycline. They are really
20 focused towards amphetamines and amphetamine salts.

21 30 milligrams IR and 10 milligrams DR, not even
22 talked about in those patents.

23 There is no method of treating rosacea or other
24 inflammation other than attention deficit. And there is no
25 claimed steady state blood levels. The more, the better, in

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1 terms of the amphetamines.

2 Q. Are you aware that Dr. Friend opines that Shire
3 basically copied the Adderall XR formulation and just
4 replaced doxycycline for the amphetamines?

5 A. I am aware of that.

6 Q. How would you respond to that opinion?

7 A. I disagree. I mean, these are completely different
8 products. A formulator would not just think that the
9 amphetamines are equivalent to doxycycline.

10 Q. Are you familiar with Dr. Friend's opinion that Shire
11 Labs and other development companies had what he calls
12 toolkit technologies that they could use to develop almost
13 any drug?

14 A. Well, you know, every firm has got technologies that
15 they are more capable of and facile with than others. But
16 every drug is its own challenge. Every drug development
17 project has got its own objectives. You have to take into
18 account absorption characteristics, where it's being
19 absorbed, is there an absorption window, what are the plasma
20 concentrations I am trying to hit.

21 One size doesn't fit all. I think most folks
22 that have been through multiple product developments would
23 say, you have got to take each drug at its own.

24 Q. Let's turn to your next slide, the 226, and the next
25 group of references cited by Dr. Friend. What are the

Rudnic - direct

1 references that you have called Other References here?

2 A. Well, these references are hard to pack into one
3 category. So I just put them all as other. There is a Joe
4 Swintosky article about spansules, 1963.

5 There is the '304 patent and the '766
6 publication, which I am very familiar with because I am the
7 lead inventor on that publication.

8 Q. Did you review each of those references in your
9 opinion?

10 A. I did.

11 Q. If we can discuss them individually. Your next slide
12 is 227. What is the subject matter of the Swintosky 1963
13 reference?

14 A. He discloses formulations with effective therapy from
15 8 to 12 hours.

16 Joe Swintosky published this paper very early in
17 controlled release development.

18 Q. Have you formed an opinion regarding whether the
19 Swintosky reference anticipates or renders the inventions of
20 the Chang patent obvious?

21 A. I have. I believe it does not.

22 Q. What is the basis of your opinion?

23 A. Well, again, in the Swintosky article, he doesn't
24 disclose, he doesn't teach or even suggest doxycycline. He
25 doesn't think about a -- a once-a-day formulation is never

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1 mentioned. Claimed steady state blood levels are irrelevant
2 in this article. They are not even contemplated. And
3 treating rosacea isn't even mentioned.

4 Q. Let's turn to your next slide, 228. What is the
5 subject matter of the '304 patent?

6 A. Well, this is a once-daily formulation of an
7 antibiotic dose of minocycline where the immediate release
8 and delayed release portion are each antibiotic.

9 Q. How is the '304 patent relevant to the formulation of
10 the doxycycline drug without antibiotic effect?

11 A. It's not.

12 Q. What is the basis of your opinion?

13 A. Well, in the '304 patent, again, it is an effective
14 antibacterial therapy. What they are trying to do is have a
15 better antibacterial product. And what they have done is
16 they have said that the minimum concentration, that's the
17 trough levels, have to be in the .1 to 1 range. But there
18 is no limit on C_{max} . What they are saying is the minimum has
19 to be above .1, if you will. But there is no limit on the
20 maximum.

21 The immediate release and delayed release
22 portions are each supposed to be independently antibiotic.
23 Whereas with the Chang patent you have no antibacterial
24 effect. The entire therapeutic activity, in other words,
25 all the blood levels, have to be between .1 and 1 micrograms

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1 per ml. And even if you combined the immediate release and
2 delayed release portions, they should have no antibiotic
3 effect.

4 Q. Have you formed an opinion regarding whether the '304
5 patent renders the inventions of the Chang patent obvious or
6 anticipates them?

7 A. I have. I believe it does not.

8 Q. Let's turn to your next slide, 229. Can you explain
9 the basis of your opinion for us?

10 A. Well, it doesn't disclose, teach, or even suggest a
11 formulation of doxycycline. They don't claim any steady
12 state blood levels, just a minimum. They have doses or
13 portions of doses, they all have to have an antibiotic
14 effect. Their maximum plasma concentrations are, you know,
15 limitless. And they don't disclose a 30 milligram or a ten
16 milligram IR/DR combination. And they don't mention
17 treating rosacea.

18 Q. Let's turn to the next reference cited by Dr. Friend.
19 Can you generally describe for us the subject matter of the
20 '766 publication?

21 A. I know this one well. I am the lead inventor of this
22 technology. This ultimately became an issued patent in
23 2004. This is an improved antibiotic formulation for
24 doxycycline.

25 Q. How is it relevant to the inventions of the Chang

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1 patent?

2 A. It's not.

3 Q. Can you describe that for us?

4 A. Well, in this particular patent, our goal was
5 multiple pulses of antibiotic to improve the antibiotic, or
6 the killing ability of the antibiotic towards the bacteria.
7 What we found is that by giving multiple pulses, three or
8 more, that we can actually improve the antibacterial
9 activity of an antibiotic.

10 So our goal is always to take an antibiotic dose
11 and make it even more so, more effective.

12 So we use those pulses to create multiple C_{max}
13 concentrations. And the last thing we wanted to do was have
14 a steady state plateau. What we found, and what we were
15 trying is by avoiding a steady state plateau, you improve
16 the antibacterial activity.

17 Chang, however, has no antibiotic effect. His
18 maximum C_{max} of one micrograms per ml is well below where we
19 were operating. And the goal for Chang was a steady state
20 plateau, directly opposite of what I was trying to
21 accomplish back in that time period.

22 Q. Let's turn to your next slide. Have you formed an
23 opinion regarding whether the '766 publication renders the
24 inventions of the Chang patent obvious or anticipates those
25 inventions?

Rudnic - direct

1 A. I believe it does not.

2 Q. Let's turn to the tab in your binder that has been
3 labeled as PTX-479. What is this document?

4 A. This is the notice of allowance of claims from the
5 Patent and Trademark Office for the Chang patent.

6 Q. Did you review this document in connection with
7 forming your opinions?

8 A. I have.

9 MS. WILLGOOS: Your Honor, we would like to move
10 PTX-479 into evidence.

11 MR. STEUER: No objection.

12 THE COURT: It is admitted.

13 (Plaintiffs' Trial Exhibit No. 479 received in
14 evidence.)

15 BY MS. WILLGOOS:

16 Q. Do you know whether the Patent Office considered the
17 '766 prosecution publication during the prosecution of the
18 Chang patent?

19 A. It is my understanding they did.

20 Q. How did the Patent Office consideration of this
21 reference impact your opinion? Turn to the next reference.

22 A. It was considered the closest prior art by the PTO.
23 Yet the Chang patent was issued over this publication. And
24 the patent examiner, at the bottom highlight, says, This
25 application does not teach or fairly suggest dosing forms

Rudnic - direct

1 comprising about 40 milligrams doxycycline.

2 I agree that this application has nothing to do
3 with what Chang accomplished.

4 Q. Let's turn to the next group of references, the
5 Periostat references. Slide 233. What is the Periostat
6 label?

7 A. The Periostat label is basically the FDA approved
8 labeling for twice daily dosing for the treatment of
9 periodontitis, which is an inflammation of the gums.

10 Q. What are the Walker 2000 and Thomas 2000 references?

11 A. These are microbiology studies of Periostat.

12 Q. Did you review all three of these references in
13 connection with your opinions in this case?

14 A. I have.

15 Q. Let's turn to your next slide, 234. In your opinion,
16 do the Periostat references anticipate or render obvious the
17 inventions of the Chang patent?

18 A. No, they don't.

19 Q. What is the basis of your opinion?

20 A. Well, they don't disclose, they don't teach or even
21 suggest, one more time, once-daily formulation. They don't
22 talk about a claimed steady state blood level of this drug,
23 or any drug. There is no minimum or maximum serum
24 concentrations. They certainly don't disclose 30 milligrams
25 immediate release or 10 milligrams delayed release and they

Rudnic - direct

1 don't discuss anything about a method of treating rosacea.

2 Q. Let's turn to the next reference that Dr. Friend
3 relies on, Slide 235, the Ashley 2002 slide deck.

4 MS. WILLGOOS: Your Honor, at this point I would
5 like to note that plaintiffs object, actually, to this
6 particular document being moved into evidence. By speaking
7 about it we still intend to reserve that objection.

8 THE COURT: That is noted.

9 MS. WILLGOOS: Thank you.

10 BY MS. WILLGOOS:

11 Q. Can you generally describe for me what the Ashley
12 2002 slide deck is?

13 A. I don't know definitely what it is. But it appears
14 to be a CollaGenex corporate overview. I am not sure what
15 the purpose of its existence or use is.

16 Q. Okay. Do you know if it's publicly available?

17 A. I believe it's not publicly available. And when I
18 tried to search for it, I can't find it.

19 Q. What types of formulations are disclosed in the
20 Ashley 2002 slide deck?

21 A. It's basically talking about some studies with
22 Periostat, as far as I can tell, and some other corporate
23 information, but it's not directed to a once daily
24 formulation of doxycycline.

25 Q. And have you formed any opinion regarding whether the

Rudnic - direct

1 Ashley 2002 slide deck renders obvious the inventions of the
2 Chang patent or anticipates those inventions?

3 A. I have, and I believe it does not.

4 Q. Let's turn to the next slide and discuss
5 Dr. Feldman's use or alleged use of Periostat.

6 Dr. Rudnic, who is Dr. Feldman?

7 A. I believe he is a dermatologist.

8 Q. And have you reviewed the patient record of
9 Dr. Feldman?

10 A. I have.

11 Q. Do you know if it's publicly available?

12 A. I don't believe it is.

13 Q. Okay. And what is the basis of your opinion?

14 A. That it's not publicly available?

15 Q. Yes, that's correct.

16 A. I can't find it when I search for it.

17 Q. Okay. Let's turn to your next slide.

18 Have you formed an opinion regarding whether the
19 patient record anticipates or renders obvious the inventions
20 of the Chang patent?

21 A. Yes, I have.

22 Q. And what is your opinion?

23 A. I believe that the art -- the slide just switched.

24 Are we on?

25 Q. Sorry. We were talking about Dr. Feldman's alleged

Rudnic - direct

1 use. Do you have an opinion whether Dr. Feldman alleged use
2 of Periostat renders obvious the invention on the Chang
3 patent?

4 A. Yes, I do, and it does not. It's not a public
5 document, and it doesn't talk about any formulations. It
6 doesn't talk about a steady state blood level. It doesn't
7 talk about any maximum or minimum concentrations, and it
8 certainly doesn't disclose the formulation of a 30-milligram
9 IR or 10-milligram DR portion. So it's just kind of
10 irrelevant.

11 Q. Okay. How does a person of ordinary skill in the art
12 of formulation normally use patient records when making a
13 drug formulation?

14 A. They don't. I worked on over 100 formulation
15 projects. I have commercialized over 80 projects. I've got
16 over 50 U.S. patents. I've never once seen a patient record
17 in developing a product.

18 Q. Okay. Now, according to Mylan's expert, Dr. Friend,
19 a person of ordinary skill in the art in the 2000 and 2003
20 time period would have been motivated to combine a lot of
21 the subsets of the art we just discussed in order to come up
22 with the inventions of the Chang patent.

23 What is your opinion on that point?

24 A. Well, it's a retrospective look. He is taking a look
25 at the literature through the lens of the Chang patent. He

Rudnic - direct

1 starts there and he looks backwards. So ...

2 Q. Let's turn to your next slide.

3 And what is the basis for your opinion that a
4 person of ordinary skill would not have come up with these
5 inventions?

6 A. Well, the art teaches away, and, you know, it's a lot
7 like when if you start with a formulation and process that
8 tells you how to get there and then you look backwards and
9 look for snippets in previous articles that kind of sound
10 like things that you see in this one recipe or article, it's
11 kind of like looking at a recipe for a souffle and going
12 back and finding a recipe that has butter, one that has eggs
13 and one that has flour. The problem is that what you are
14 looking at are recipes for a loaf of bread or a cookie or a
15 tortilla. Well, if you did it prospectively, somebody who
16 is looking at making a tortilla is not going to be looking
17 at making a souffle and they're not going to look at
18 combining everything else on how to do it. So there is a
19 lot of hindsight that going on here.

20 Q. We've discussed Dr. Friend 's opinions. Did you also
21 consider the opinions of Mylan's pharmacokinetics expert,
22 Dr. Rubas?

23 A. Yes.

24 Q. Let's, if we can, quickly call out one of those
25 opinions in the Rubas report. For reference, we can put

Rudnic - direct

1 that up on the screen.

2 Do you recall specifically Dr. Rubas's opinion
3 that one of ordinary skill could predict that a 40-milligram
4 IR product would meet the steady state claim limitations
5 claimed in the Chang patent about 0.1 to 1.0 micrograms per
6 milliliter?

7 A. Yes, I read that.

8 Q. Let's call up the next opinion. Actually, I think
9 they're both up there by Dr. Rubas.

10 Do you also recall his opinion that one of
11 ordinary skill could predict an IR-to-DR ratio to meet that
12 steady state range?

13 A. I remember reading that.

14 Q. And do you agree with these opinions?

15 A. No, I don't.

16 Q. Let's turn to slide 28.

17 Can you briefly explain for us why you disagree
18 with Dr. Rubas's opinions?

19 A. Well, first of all, it's unclear to me whether a
20 40-milligram immediate release would stay below a maximum
21 plasma concentration of one microgram per mil, and I don't
22 believe that he can predict especially with the precision
23 that he claims that he can.

24 Q. Why?

25 A. And --

Rudnic - direct

1 Q. I'm sorry. Why does it matter whether or not the
2 blood level stays below 1.0 micrograms per litter?

3 A. Well, if it's going above 1, it starts to have an
4 antibacterial effect, which means your formulation is
5 unacceptable from a clinical perspective.

6 Q. Let's turn to the next slide.

7 What do you mean when you say Dr. Rubas relies
8 solely on mean data?

9 A. Well, he takes a look -- I mean he does a lot of
10 modeling, so let's remember that. A lot of the numbers he
11 is coming up with are not real. They are mathematical
12 projections of data that have been lifted for various
13 portions of the literature. And when you do that, you
14 ignore variability, you ignore the natural variation that
15 happens in a clinical population. So to focus on means and
16 only on means ignores quite a bit of the story. So we start
17 there.

18 Q. Okay. And what specifically -- why does it matter
19 that he ignores the individual patient data?

20 A. Well, for example, if you are putting up very close
21 to one microgram per mil, and you're estimating that you are
22 very close to that, there is a good portion of population
23 that will be within two standard deviations beyond that that
24 are going to be well above 1. So a good portion of the
25 population will fail.

Rudnic - direct

1 And, again, I don't agree with some of the
2 numbers that he has, but even if you took them at face
3 value, a good portion of the population will be above 1 with
4 his analysis.

5 Q. Let's move on to the next point. If you can turn in
6 your exhibit binder to DTX-1847.

7 A. Yes.

8 Q. Can you tell us what this document is?

9 A. Well, this is the product labeling for Periostat
10 tablets.

11 Q. Did you review this document in connection with
12 forming your opinions in this case?

13 A. I have.

14 Q. Can you next turn to PTX-221 and tell us what that
15 document is?

16 A. That is the product labeling for Periostat capsules.

17 Q. And did you review this document as well?

18 A. I have.

19 MS. WILGOOS: Your Honor, at this time Galderma
20 would like to move into evidence DTX-1849 and PTX-221.

21 THE COURT: 1847?

22 MS. WILGOOS: I'm sorry. 1847.

23 THE COURT: Any objection?

24 MR. STEUER: No, your Honor.

25 THE COURT: They're admitted.

Rudnic - direct

1 (PTX No. 221 and DTX No. 1847 received into
2 evidence.)

3 BY MS. WILGOOS:

4 Q. Dr. Rudnic, does Dr. Rubas rely on these two
5 documents in forming his opinion?

6 A. No, he only relies on one of them. He selected the
7 one with Periostat tablets, which has a lower Cmax, about
8 10 percent lower than Periostat capsules. And I will remind
9 you that Oracea is a capsule as well; and, quite frankly,
10 the capsule data was probably the more appropriate data to
11 start looking at.

Q. Why does it matter what Cmax he chose?

13 A. Well, when you are modeling from a single dose and
14 this Cmax is from a single dose and you go to a multiple
15 dose, and I showed you in the slide earlier, the Cmax will
16 go up, and because this is half the dose, by picking a lower
17 Cmax, you are more likely to stay under 1, which, if that is
18 your goal for your analysis, then you want to pick the
19 lowest Cmax possible.

I think picking a higher Cmax or the more appropriate Cmax of the Periostat capsules would have given him a 10 percent higher number, which would have been much more closer to breaking that 1 limit. Plus, it would have put a lot more people in that population well above 1.

25 Q. Okay. And what half-life for doxycycline did

Rudnic - direct

1 Dr. Rubas use in his analysis?

2 A. Well, he picked 17.5 hours, and it's a mystery to me
3 how he selected it. If you read his deposition, it appears
4 as though he created a model out of the Periostat data which
5 gave him a 17 and-a-half hour half-life which was shorter
6 than the half-life from the data originally gave him. And
7 if you look at the literature values, the half-life should
8 be somewhere in the 20-to-24 hour range, not 17 and-a-half.

9 Q. Okay. What impact, if any, would Dr. Rubas's
10 selection of the lower half-life have on his analysis?

11 A. Well, the half-life impacts how much drug is
12 remaining for subsequent doses to be accumulated into those
13 other doses, which pushes up the peak level. So by picking
14 a shorter half-life than one even exists on all the data
15 that he is looking for, what he has done is he has further
16 biassed the data to be low. Had he picked a normal
17 half-life, his means would have been above 1, I believe, and
18 certainly a majority of the population would have been above
19 1 at the Cmax.

20 Q. Let's turn to your next slide.

21 And can you describe for us how Dr. Rubas's
22 opinions impacted your own opinions in this case?

23 A. I've considered them, but I don't agree with his
24 conclusions.

25 Q. Okay. And why don't you agree?

Rudnic - direct

1 A. Well, again, he starts with the invention of the
2 Chang patent. He looks at the Chang patent, he looks at
3 Oracea, and he assumes the only problem to be solved is the
4 ratio of the immediate release and delayed release as though
5 that were the only issue in front of these people developing
6 this product. He fails to consider how to formulate
7 doxycycline, and even in his deposition, he didn't know
8 there was an absorption window and he even fails to consider
9 the impact of an absorption window on his model.

10 Q. Okay. Let's turn to your next slide.

11 Are there any other factors that you believe
12 support your opinions regarding validity?

13 A. Well, I believe there was a long unmet clinical need
14 for this product. And the fact that it is a commercial
15 success is a testimonial to that.

16 Q. What about unexpected results? Do you believe there
17 are any unexpected results of the Chang patent?

18 A. I believe so. I think that if I were given this task
19 at the beginning of the assignment, I wouldn't have expected
20 that an IR/DR would have succeeded given an absorption
21 window. I would have taken another approach.

22 Q. Let's talk about the last bullet point, failures of
23 others. Who attempted to formulate doxycycline in a dose
24 without antibiotic effect?

25 A. Well, there was a very fine formulation company

Rudnic - direct

1 called Faulding. It's an Australian firm that had worked
2 with CollaGenex to develop a sustained release product of
3 doxycycline.

4 Q. Okay. Can you please turn to PTX-530 in your exhibit
5 binder?

6 A. Yes.

7 Q. And did you review this document in connection with
8 your opinion?

9 A. Yes.

10 Q. Can you please turn to PTX-95?

11 A. Yes.

12 Q. What is this document?

13 A. This is a discussion of the completion of enrollment
14 for the clinical study, which is the protocol that we saw
15 previously, and a little bit of stability data along with
16 it.

17 Q. Can you turn to the next tab, PTX-96, and tell us
18 what that document is?

19 A. This is a communication regarding clinical failure of
20 the Faulding results. Very low bioavailability.

21 Q. And PTX-510 in your binder. Can you look at that one
22 and tell us what that is?

23 A. That is an internal CollaGenex communication talking
24 about the clinical failure.

25 Q. Did you review each of these documents in forming

Rudnic - direct

1 your opinions?

2 A. I have.

3 MS. WILGOOS: Galderma -- I'm sorry, your Honor.

4 At this time, Galderma would like to move into evidence
5 PTX-530, PTX-95, PTX-96, and PTX-510.

6 MR. STEUER: No objection.

7 THE COURT: They are all admitted.

8 (PTX-530, PTX-95, PTX-96, and PTX-510 received
9 into evidence.)

10 BY MR. FLATTMANN:

11 Q. Dr. Rudnic, what type of formulation did Faulding
12 make?

13 A. They made a sustained release formulation, which is
14 the appropriate formulation to make for this product right
15 off the bat.

16 They tried to slow release with various rates
17 and they incorporated organic acids which would give the
18 drug a best chance of being absorbed.

19 Q. And did their formulations work?

20 A. No, it was a pretty righteous failure in that the
21 best of the three formulations they tried had a 50 percent
22 extent of absorption and the other two were down around
23 30 percent.

24 Q. What do you mean when you say "extent of absorption?"

25 A. The amount of drug absorbed, you know, if it were to

Rudnic - direct

1 be consistent with the immediate release product they were
2 comparing it to, would be close to 100 percent.

3 By having the best product at 50 percent means
4 half the drug is going down to the lower parts of the GI
5 tract, which is going to impact the bacteria and the flora
6 in the lower GI tract, which can give you, you know, all
7 sorts of significant problems.

8 Q. Okay. Dr. Rudnic, are you aware Mylan argues that
9 CollaGenex and not the Chang inventors are the real
10 inventors of the Chang patent?

11 A. Yes, I heard that.

12 Q. How do you respond to that?

13 A. I just disagree.

14 Q. Okay. Let's turn to your next slide. And can you
15 explain for us the basis of your disagreement?

16 A. Well, you know, when you look at all the documents
17 that I have looked at, it's pretty clear that CollaGenex
18 gave the Chang inventors a broad goal. Here is some of the
19 things we would like to achieve. A target, if you will.

20 They didn't tell them how to achieve it. They
21 didn't tell them how to formulate it. They didn't tell them
22 how to combine materials or they didn't tell them what to
23 select. That was their choice.

24 What CollaGenex told Chang and the inventors was
25 here is the kind of product, you know, that we would like to

Rudnic - direct

1 have, but not even in all the greatest detail that Chang
2 ended up.

3 Q. Okay.

4 A. And --

5 Q. I'm sorry. Go ahead. I was just going to ask you
6 what you used? What materials you used in forming your
7 opinion?

8 A. Well, I looked at the Ashley deposition and the
9 inventors depositions as well as other documents that have
10 been supplied to me, you know, in review of this case. And
11 Ashley testified that CollaGenex, you know, had no knowledge
12 of formulation, which I understand because I knew CollaGenex
13 back when I was the CEO at Middlebrook. They weren't a
14 formulation company, and they relied on Shire Labs's
15 expertise to develop this formulation. And when I look at
16 the depositions of the inventors, they testified that they
17 invented the formulation.

18 Q. Okay. Let's turn to your next slide, and just to
19 summarize your opinions.

20 What were you doing in the 2000 and 2003 time
21 frame, Dr. Rudnic?

22 A. I was the CEO and intellectual founder of
23 Middlebrook, which was a company I took public as the
24 intellectual founder and CEO, and I ended up taking it
25 public on the NASDAQ in October of 2003, but we were well

Rudnic - cross

1 on our way in 2002 and into 2003.

2 We were developing antibiotic products that
3 were improved antibacterial activity, so I was right in the
4 middle of antibiotics, antibiotic development. We had world
5 class antibiotic advisers on our staff, so we were right in
6 the middle of the antibiotic world.

7 Q. So do you agree with Mylan's counsel when he said
8 in his opening statement that coming up with the Chang
9 formulation was a simple pedestrian formulation exercise?

10 A. I can't believe I didn't think of it. I mean get
11 around, and I hadn't heard of it, and it certainly wasn't
12 obvious to me. And even when I saw the product Oracea and
13 the Chang patent and what they accomplished, I would have
14 loved to have this product in our portfolio back when I was
15 the CEO of that company. Believe me, if that technology was
16 so obvious to use, I would have thought of it.

17 MS. WILGOOS: Thank you for your opinions,
18 Dr. Rudnic. I have no further questions.

19 THE COURT: Thank you. Cross-examination.

20 MR. STEUER: Thank you, your Honor.

21 (Binders passed forward.)

22 CROSS-EXAMINATION

23 BY MR. STEUER:

24 Q. Good afternoon, Dr. Rudnic.

25 A. Good afternoon.

Rudnic - cross

1 Q. Dr. Rudnic, you are not a medical doctor; correct?

2 A. That's correct.

3 Q. You have never been licensed to treat patients or
4 prescribe medicines; correct?

5 A. That is correct.

6 Q. You worked for many years as an officer of Shire;
7 correct?

8 A. I was an officer of pharmacy in Shire Laboratories
9 for a short period of time, yes.

10 Q. Shire is the assignee of the Chang patent; correct?

11 A. I was not at Shire when that was assigned.

12 Q. You noticed that when you examined the patent,
13 though; right?

14 A. Yes.

15 Q. And you have been acquainted with Richard Chang, the
16 first named inventor, for many years; isn't that right?

17 A. I have.

18 Q. In fact, you have collaborated with Richard Chang on
19 patents; correct?

20 A. That's correct.

21 Q. Now, the original goal of the Oracea development
22 program by CollaGenex was to create a product line extension
23 that could be patented to protect the Periostat franchise;
24 correct?

25 A. I don't know that.

Rudnic - cross

1 Q. Okay. Let's look at Exhibit 1315.

2 And this is a document that you have reviewed
3 before?

4 A. Yes.

5 MR. STEUER: I offer Defendant's 1315.

6 MS. WILGOOS: No objection.

7 THE COURT: It's admitted.

8 (DTX No. 1315 received into evidence.)

9 BY MR. STEUER:

10 Q. Okay. Do you see there is a number two there that
11 says once-a-day Periostat development?

12 A. Yes.

13 Q. And it talks about the objectives of the program?

14 A. Yes.

15 Q. And it says: Develop proprietary once-a-day
16 Periostat formulation that could be patented worldwide,
17 protecting the Periostat franchise and enabling us to
18 develop other potential indications for the chronic
19 administration of doxycycline.

20 Do you see that?

21 A. Yes.

22 Q. Do you understand that to be the goal of the Oracea
23 development program, or one of them at least?

24 A. I read that to be a statement from somebody working,
25 you know, on the project.

Rudnic - cross

1 Q. Do you have any reason to believe it's false?

2 A. No.

3 Q. If you look to the last paragraph on that first page,
4 do you see it says: Major players in the sustained release
5 field such as Elan Pharmaceuticals charge significant access
6 fees for their technology, which are outside the scope of
7 the available budget at present.

8 Do you see that?

9 A. Yes.

10 Q. And is it your understanding that in May of 2001,
11 CollaGenex could not afford Elan Pharmaceuticals?

12 A. I don't know that for a fact. But that would be a
13 reasonable reading of that.

14 Q. And Shire positioned itself as a less expensive
15 formulation company. Isn't that correct?

16 A. No.

17 Q. So we agree that it was a less well known player than
18 Elan?

19 A. Elan licensed some products from Shire. I am not
20 entirely sure it was unknown. But less known. Elan was
21 pretty newsworthy for blowing up financially. But I will
22 say that they were probably less known.

23 Q. Now, you testified that Oracea met a long-felt need
24 for a once-daily doxycycline product. Correct?

25 A. Yes.

Rudnic - cross

1 Q. In fact, doxycycline is a drug that has been used as
2 a once-a-day medicine for many years. Isn't that correct?

3 A. No.

4 Q. All right. Let's look at your deposition, if we may.
5 If we may have a copy of the deposition for the Court. I
6 think it's in the front binder.

7 If you look at Page 57 of Dr. Rudnic's
8 deposition, please.

9 A. Is this under the heading Transcript?

10 Q. Yes.

11 Starting on Line 17, I say: "All right.

12 "And do you see that after the first day, it
13 allows a maintenance dose of a hundred milligrams a day that
14 can be administered as a single dose or as 50 milligrams
15 every 12 hours?"

16 And you say, "Yes, I see that."

17 Then the question was:

18 "Okay. Does that -- does that allow for a
19 single dosage of doxycycline as a maintenance dose?"

20 And you can read your answer there. But I think
21 you agree that that is what the label says. Is that fair?

22 A. Well, it's --

23 MS. WILLGOOS: Objection. Improper impeachment.

24 THE COURT: Mr. Steuer, are you still trying to
25 impeach the witness?

Rudnic - cross

1 MR. STEUER: Yes. I am asking if that reminds
2 him that there is a single dose available.

3 MS. WILLGOOS: There is also a deposition --

4 MR. STEUER: I don't have to read it to him to
5 impeach him.

6 THE COURT: Is this the portion that you believe
7 is inconsistent with testimony he just gave?

8 MR. STEUER: Yes. I can read.

9 BY MR. STEUER:

10 Q. If you look at the second paragraph there, Doctor --

11 THE COURT: I am asking you, is that the part
12 that is inconsistent or are you trying to refresh his
13 recollection?

14 MR. STEUER: Right now I am trying to refresh
15 his recollection. He testified he was aware of once-a-day
16 preparations at his deposition. So I was asking him to take
17 a look.

18 THE COURT: Ms. Willgoos.

19 MS. WILLGOOS: If he has a question to impeach
20 the witness he can use it. Refreshing the recollection of
21 what he previously testified about, particularly when he was
22 talking about a document in the deposition that the witness
23 does not now have in front of him, I don't believe that is
24 proper impeachment, Your Honor.

25 THE COURT: Okay. Mr. Steuer, why don't we

Rudnic - cross

1 start this over again and let's be clear on whether you are
2 trying to refresh his recollection or impeach him.

3 BY MR. STEUER:

4 Q. Fair enough. Let me pose a new question.

5 Dr. Rudnic, you are aware that labels for
6 existing doxycycline products before Oracea allowed
7 maintenance doses to be administered once daily. Correct?

8 A. That's what the label says, yes. But I can tell
9 you --

10 Q. That's all I asked.

11 A. I am going to finish my answer.

12 THE COURT: It appeared you had finished your
13 answer at that point. Let's let Mr. Steuer go ahead.

14 BY MR. STEUER:

15 Q. You understand that doxycycline was available as a 50
16 milligram or 100 milligram dose form prior to April 2003.
17 Right?

18 A. Yes.

19 Q. And you were here when Dr. Webster testified?

20 A. Yes.

21 Q. And did you see that he had published articles that
22 said that 50 or a hundred milligrams of doxycycline could be
23 administered once or twice a day?

24 A. Yes. Well, what I saw was that it was perhaps
25 labeled to take that way, and as I understand and remember

Rudnic - cross

1 he said that may have been put in by an editor and may not
2 have actually been what he put in.

3 But what I was trying to get across just before
4 is that just because it's in the label doesn't mean that
5 that is how it's used.

6 When I was the CEO of Middlebrook, we bought
7 Keflex, which was invented about the same time as
8 doxycycline by Pfizer. It was labeled for once-a-day use.
9 But nobody used it for once-a-day use because it was
10 ineffective.

11 When you ask me use, I say no. It's in the
12 label, yes.

13 MR. STEUER: Move to strike as nonresponsive.

14 THE COURT: I will not strike it. But I will
15 ask the witness to please respond to the question that is
16 asked. You will have a chance on redirect to give further
17 explanation.

18 BY MR. STEUER:

19 Q. Did you also hear Dr. Webster testify that he
20 sometimes prescribed doxycycline once every two days?

21 A. Yes.

22 Q. He didn't blame that on the publisher. Right?

23 A. No, he didn't.

24 Q. So a once-a-day doxycycline or even a
25 once-every-two-day doxycycline did not appear to be a

Rudnic - cross

1 long-felt need for Dr. Webster, did it?

2 A. I am not going to opine as to what Dr. Webster
3 thought.

4 Q. Dr. Rudnic, you testified about the absorption
5 window. Do you recall that?

6 A. Yes.

7 Q. At some length. In fact, it's been well known ever
8 since doxycycline was discovered that the drug is primarily
9 absorbed in the duodenum. Isn't that correct?

10 A. That part was well known, yes.

11 Q. And this is a function of the pH of the environment
12 in the digestive system. Correct?

13 A. Not necessarily.

14 Q. Not necessarily. What does that mean?

15 A. Well, actually, I believe that to be false.

16 Q. So you disagree with that.

17 A. Yes.

18 Q. Who has disproven that?

19 A. I believe Faulding pretty much proved it false. The
20 Faulding failure pretty much proves it false.

21 Q. We will talk about that. It was well known before
22 the Chang patent that doxycycline's maximal liposolubility
23 is at a pH of 5.5. Correct?

24 A. Right.

25 Q. You are not aware of any references prior to Chang

Rudnic - cross

1 that tell you that doxycycline was absorbed in the lower
2 regions of the small intestine or the colon. Correct?

3 A. That's correct.

4 Q. And you are not aware of anyone who thought
5 doxycycline was absorbed throughout the intestinal tract.
6 Correct?

7 A. Can you repeat that question?

8 Q. You are not aware of anyone who thought doxycycline
9 was absorbed throughout the intestinal tract. Correct?

10 A. There are some reports in the literature that say it
11 is very well absorbed -- they don't mention the duodenum.
12 And they talk about it being essentially fully absorbed,
13 with no discussion of where in the GI tract.

14 In the 2000 to 2003 time frame, there are about
15 ten to 15 of those publications.

16 So I would have to say I would disagree with
17 that.

18 Q. Could we please put up Page 159 of Dr. Rudnic's
19 deposition, we will go over to 160 at the bottom:

20 So I want to know that prior to whatever
21 investigation Shire did, are you aware of anyone who
22 believed that, in fact, doxycycline was well absorbed in
23 those areas of the intestine?

24 Answer: I'm not aware of anyone that believes
25 that they were absorbed throughout the intestinal tract.

Rudnic - cross

1 In fact, Dr. Rudnic, the region specific
2 absorption of doxycycline was well known to Shire from the
3 outset of the once-a-day project. Correct?

4 A. It was not -- at the outset of the project or the
5 outset that Shire was involved?

6 Q. Certainly at the outset of Shire's involvement?

7 A. At the outset of Shire's involvement, it was known,
8 yes, but only to Shire.

9 Q. Shire was the only one that knew that?

10 A. Well, CollaGenex, the folks at Scintipharma. But it
11 was not publicly known.

12 Q. When was the region absorption project done?

13 A. Well, it was -- the study was completed in February
14 of '03. It was started in June of '02. I don't know when
15 they had any interim data that would suggest it. But my
16 guess, it was sometime in late '02.

17 Q. Could you please turn to DTX-1312. Is this a
18 document you reviewed in preparing your opinion?

19 A. Yes.

20 MR. STEUER: I offer DTX-1312.

21 THE COURT: Any objection?

22 MS. WILLGOOS: No objection.

23 THE COURT: It's admitted.

24 (Defendants' Trial Exhibit No. 1312 received in
25 evidence.)

Rudnic - cross

1 BY MR. STEUER:

2 Q. You see that this is an internal Shire memorandum?

3 A. Yes.

4 Q. You see it's dated October 14th, 2002?

5 A. Yes.

6 Q. And if you look at the last sentence of the third
7 paragraph, it says, In other words, if we state to
8 CollaGenex that we did our part by simply confirming that
9 doxycycline has region specific absorption, Rob will
10 disagree. We need to be careful with this issue.

11 Do you see that?

12 A. Yes.

13 Q. That's before there was any report from the study
14 that you have referred to. Correct?

15 A. I don't know that. There is no evidence that I saw
16 as to when Shire had this information. I know that the
17 study kicked off in June, and the final study report was
18 compiled in February, somewhere in there results were known.
19 It's unclear as to when exactly that is.

20 Q. And Shire didn't commission that report. Correct?

21 A. CollaGenex commissioned the absorption report, yes.

22 Q. Now, it's your understanding that the delayed release
23 portion of Oracea has a rapid and immediate release two to
24 three hours after ingestion. Correct?

25 A. A delayed rapid release, yes.

Rudnic - cross

1 Q. So you have the immediate release beadlets?

2 A. Yes.

3 Q. And you have the delayed release beadlets. And it is
4 your understanding that the delayed release beadlets are
5 going to burst out the doxycycline in two to three hours?

6 A. Two to three hours after the immediate release but
7 within four hours, yes.

8 Q. Two to three hours after ingestion?

9 A. Yes.

10 Q. And at that point, the delayed release portion will
11 be released into the duodenum. Correct?

12 A. Not necessarily.

13 Q. That's the expectation, isn't it?

14 A. That's the expectation, but it's not necessarily so.
15 Some of those pellets can go well beyond the duodenum to the
16 jejunum, depending upon how fast the transit is.

17 Q. Some of them can be excreted for that matter.

18 Correct?

19 A. It would be a remarkable excretion in two hours.

20 But, yes.

21 Q. So you are not going to get an absorption, at least
22 any meaningful absorption, outside the duodenum, of any part
23 of the pill. Correct?

24 A. No, that's not true.

25 Q. So you think that it will be absorbed meaningfully

Rudnic - cross

1 below the duodenum?

2 A. Well, if you look at the results of that study, there
3 was eight subjects. Eight normal volunteers. Two of them
4 had almost no absorption after the duodenum. It was very,
5 very low. Maybe ten percent of what you saw in the
6 duodenum. And almost nothing in the colon. But six of the
7 eight had about half of the absorbability that you saw in
8 the duodenum in the jejunum, in the early part of the ileum.
9 So I would say it was, you know, definitely a window. But
10 you had some absorption.

11 But for two -- you know, two of the eight, it
12 was an iron curtain slamming down on the absorption. But
13 for six of the eight it was about half as much. And then
14 there was even one of the eight where they showed about 15
15 percent absorption in the colon, which is remarkable.

16 Q. The inventors, the concept of the invention was to
17 have a delayed release in the duodenum. Correct?

18 A. I would believe that the goal would have been to
19 avoid going really far down the GI tract. But duodenum,
20 probably.

21 Q. The duodenum is the top of the small intestine.
22 Correct?

23 A. Correct.

24 Q. You get beyond that, you are in the lower intestine,
25 and you have a risk of interfering with bacterial microflora

Rudnic - cross

1 for one thing. Right?

2 A. No.

3 Q. You don't. If doxycycline is in the lower intestine,
4 large amounts, it doesn't cause risk to the microflora?

5 A. If it is not absorbed, yes. You were talking about
6 the pellets. I thought you were still talking formulated
7 product that was yet to be absorbed.

8 Q. The goal is to get it absorbed and the duodenum is
9 the best place to absorb it. Right?

10 A. Absolutely.

11 Q. One of the goals of the Chang patent is to achieve a
12 steady state blood level of .1 to 1.0 micrograms per
13 milliliter of doxycycline. Correct?

14 A. That's correct.

15 Q. You haven't seen any studies to indicate that 1.0
16 micrograms per milliliter of doxycycline in the blood
17 actually is an antibiotic threshold, have you?

18 A. No.

19 Q. The Chang patent discloses that the blood levels can
20 be obtained through a single daily dose of an immediately
21 release formulation, preferably about 40 milligrams of
22 doxycycline. Correct?

23 A. I am sorry. Could you repeat that, counselor? I
24 apologize.

25 Q. That's okay. The Chang patent discloses that the

Rudnic - cross

1 blood levels can be obtained through a single daily dose of
2 an immediate release formulation, preferably about 40
3 milligrams of doxycycline. Correct?

4 A. That's correct.

5 Q. And based on your substantial experience in obtaining
6 patents that you testified to, it would likely be difficult
7 to obtain a formulation patent for a 40-milligram instant
8 release doxycycline tablet. Correct?

9 A. That's correct.

10 Q. Now, the patent makes no claim that the three-to-one
11 ratio of instant release to delayed release formula has any
12 therapeutic or safety advantages compared to a 40-milligram
13 instant release doxycycline dose. Correct?

14 A. Apologize again, counselor, could you repeat that?

15 Q. That's okay. The patent doesn't make any claim of
16 therapeutic or safety benefits from this two-portion -- this
17 two-component capsule against a 40-milligram instant
18 release. Correct?

19 A. I believe that's correct.

20 Q. And in fact, CollaGenex conducted a clinical study
21 that concluded that the doxycycline blood levels for 40
22 milligrams in the Oracea formula, three to one, were
23 comparable. Correct?

24 A. Were comparable to?

25 Q. Were comparable in terms of bioequivalency?

Rudnic - cross

1 A. To what?

2 Q. The 40-milligram dose of doxycycline, two Periostats
3 taken at once was bioequivalent to the Oracea formula of
4 three to one?

5 A. Roughly bioequivalent.

6 Q. And if I could have you look at DTX-1309, please.

7 Dr. Rudnic, this is a document that you reviewed during your
8 investigations for your report. Correct?

9 A. That's correct.

10 MR. STEUER: I offer Defendants' 1309.

11 MS. WILLGOOS: No objection.

12 THE COURT: It is it's admitted.

13 (Defendants' Trial Exhibit No. 1309 received in
14 evidence.)

15 BY MR. STEUER:

16 Q. You recognize 1309 as a report of a clinical trial in
17 which they compared Periostat twice a day, the Oracea
18 formula of three to one, and third, a single daily dose of
19 two Periostats. Correct?

20 A. That's correct.

21 Q. And if you turn to what is called Page 7 in the
22 document, the bottom right-hand number is 3073. I think I
23 am in the right place.

24 A. Yes, I have it.

25 Q. 3074, actually, the next page. The conclusion here,

Rudnic - cross

1 can you highlight that conclusion. Treatment A was twice a
2 day -- Treatment A was the 75/25 IR/DR. Correct?

3 A. Correct.

4 Q. And treatment C was 40 milligrams once a day.
5 Correct?

6 A. I believe that's right.

7 Q. And the conclusion here is that they are comparable,
8 correct, with respect to doxycycline bioavailability?

9 A. In respect to the area under the curve which is the
10 extent of absorption, yes, but they talk about higher and
11 lower C_{max} 's.

12 Q. Actually, they talk generally about bioavailability.
13 Isn't that true? And wasn't that the conclusion of the
14 report?

15 A. Yes. If bioavailability is synonymous with extent of
16 absorption, yes, then that's correct.

17 Q. Now, you mentioned the work by Faulding in 1998 and
18 1999 to develop a once-a-day Periostat product. Correct?

19 A. Yes.

20 Q. And you opined that the Faulding attempt was in your
21 words a righteous failure. Correct?

22 A. Yes.

23 Q. And you further opined that the failure by Faulding
24 shows that the Chang patent is nonobvious. Correct?

25 A. One of the things, not the only one, but one of the

Rudnic - cross

1 things.

2 Q. And, in fact, Faulding was able to produce a
3 once-a-day doxycycline product. Correct?

4 A. Not meeting the goals of the CollaGenex, you know,
5 goals that were established.

6 Q. Well, put aside CollaGenex's corporate goals. You
7 would agree that Faulding was able to produce a once-a-day
8 doxycycline product?

9 A. Not that it met .1 to one micrograms per ml.

10 Q. In fact, they did produce a once-a-day product that
11 met the limitation of .1 to 1.0 micrograms per milliliter.
12 Isn't that right?

13 A. I don't believe that's correct.

14 Q. All right. Well, let's look at your report. We have
15 got your supplemental report. I don't know if it is in
16 there. It is 1306. You can take a look at it. In
17 Paragraph 105 -- 185, pardon me. 185.

18 In 185, you say, starting three lines down, "In
19 clinical testing, the Faulding formulations did not have
20 sufficient bioavailability despite the fact that some
21 formulations had steady state blood levels of .1 to 1.0
22 micrograms per milliliter."

23 Do you see that?

24 A. Yes, I do.

25

Rudnic - cross

1 Q. Does that refresh your recollection that, in fact,
2 Faulding did produce a single daily dose product that fell
3 within the therapeutic range that is set out in the Chang
4 patent?

5 A. As I said before, that may be true, but it didn't
6 meet the goals of the project. And I'm not talking about
7 the corporate goals, I meant the therapeutic goals. By
8 having less than 50 percent of the drug absorbed, it's not
9 an effective product. It's dangerous.

10 Q. So the answer to my question "did it fall within the
11 range of the patent" is yes?

12 A. It fell within the blood levels, but it was not an
13 acceptable product.

14 Q. So you deem Faulding a failure because of a
15 bioavailability; correct?

16 A. Absolutely.

17 Q. In fact, the problem with Faulding's bioavailability
18 was that it was not bioequivalent to Periostat BID; correct?

19 A. No, it was that it wasn't fully absorbed.

20 Q. Let's look at DTX-1013, which has already been
21 admitted. I believe it's a plaintiffs' exhibit.

22 If you look at the second paragraph, I think you
23 might have even looked at that one. It says: The fastest
24 releasing dose (treatment A) is approximately 50 percent
25 available relative to the reference.

Rudnic - cross

1 Do you see that?

2 A. Yes.

3 Q. And the reference was Periostat; correct?

4 A. That's correct.

5 Q. And so it was considered a failure because it wasn't
6 bioequivalent to Periostat; right?

7 A. No, it was considered a failure because it allowed
8 unabsorbed drug to go into lower parts of the GI tract.

9 Q. That is not what it says here?

10 A. Well, that is what it means.

11 Q. Okay. That is what it means. Then it goes on to
12 say, this is confirmation of an absorption window which,
13 contrary to expectation, the addition of organic acid has
14 not significantly counteracted.

15 Do you see that?

16 A. Yes, I do.

17 Q. What absorption window are they talking about?

18 A. Well, obviously, the one with doxycycline.

19 Q. All right. The same one that you believe wasn't
20 known about until 2003?

21 A. I believe it's not publicly known about today, let
22 alone 2003, and the fact that there may be some researchers
23 somewhere with nonpublic information that might suggest that
24 there is a window doesn't tell you that there was a general
25 agreement that there was public information that there was a

Rudnic - cross

1 window.

2 Q. So your testimony is that there was just some
3 researchers somewhere with unknown information about the
4 absorption window?

5 A. No. I'm saying that if you read this literally,
6 confirmation of an absorption window, which means that
7 they -- someone had a suspicion that there was one. But
8 remember that following this, CollaGenex paid for a very
9 expensive, very specialized study to confirm that there was
10 a window. So they weren't sure what they were dealing with
11 at this point.

12 MR. STEUER: Your Honor, I don't know if I have
13 done this before, or if I should do it, but I would like to
14 move DTX-1013.

15 THE COURT: Any objection?

16 MS. WILGOOS: No objection except it was already
17 admitted as a plaintiffs' exhibit.

18 MR. STEUER: I think it's in as a different
19 number.

20 THE COURT: It's admitted before, admitted
21 again.

22 MR. STEUER: Okay.

23 (DTX-1013 received into evidence.)

24 BY MR. STEUER:

25 Q. Chang makes no claim based on bioequivalence to

Rudnic - cross

1 Periostat; correct?

2 A. That's correct.

3 Q. Based on your own experience with the FDA, you would
4 agree that it is easier to get FDA approval for a drug that
5 is bioequivalent to an existing product; correct?

6 A. As an absolute statement, I would disagree with that.

7 But as a general most of the time, yes.

8 Q. Now, the basic theory of the Faulding development was
9 to change the absorption window for doxycycline so that the
10 drug would be absorbed in the lower intestine in the colon;
11 right?

12 A. That was the idea. The reason why you put in an
13 organic acid as Faulding did is to try to eliminate any
14 possible ionization that might happen that would cause the
15 drug not to be absorbed.

16 Q. And the reason Faulding did that is because they
17 believed that if they didn't do something, it would not get
18 absorbed in the lower intestine or the colon; correct?

19 A. Not necessarily. It may have been insurance. And
20 very similar to other work that was being published around
21 that time on amoxicillin where they showed citric acid
22 helped, it didn't completely eliminate the problem but it
23 helped. And that may be what Faulding was relying on.

24 And sometimes when you are a formulator, you try
25 to give your formulation the best chance of success and you

Rudnic - cross

1 try to put as much insurance into the process early on as
2 you can. It's not necessarily a response to a known problem
3 but a perceived problem, perhaps.

4 Q. So it might not have been necessary for a known
5 problem but it was at least a response to a perceived
6 problem that without some sort of chemical modification, the
7 doxycycline would not get absorbed in the lower colon or
8 intestine; correct?

9 A. That may be a little strongly worded, but I would say
10 they're trying to give themselves the best chance.

11 Q. Okay. And although you call it a failure, doesn't
12 the fact that Faulding's product met the therapeutic blood
13 level set out in the Chang patent with a single daily dose
14 product demonstrate that even with a bad technology, it's
15 easy to produce the doxycycline that meets the blood levels
16 in the Chang patent?

17 A. If low blood levels is your only objective, then it
18 achieved it but that is not the only objective.

19 Q. Other than Faulding, are you familiar with any other
20 attempts to create a low dose doxycycline, that is, less
21 than 50 milligrams that you believe failed?

22 A. Not that I'm aware of.

23 Q. Okay. Now, Dr. Rudnic, you understand that Shire
24 told CollaGenex it planned to do the formulation of
25 once-a-day doxycycline with something it called its

Rudnic - cross

1 Microtrol technology?

2 A. I'm aware of that.

3 Q. And, in fact, the contract with Shire specified that
4 Shire would use its Microtrol technology for the
5 formulation; correct?

6 A. That is what it said.

7 Q. All right. And if you will look at 1316.

8 Do you recognize this as the contract, the
9 development agreement between Shire and CollaGenex?

10 A. Yes.

11 MR. STEUER: Your Honor, I move to admit
12 DTX-1316.

13 MS. WILGOOS: No objection.

14 THE COURT: It's admitted.

15 (DTX No. 1316 received into evidence.)

16 BY MR. STEUER:

17 Q. Okay. And then you see in the stage 1 dosage form
18 development that Shire says it will use its Microtrol
19 technology?

20 A. In that paragraph? Yes, I see it. I was looking at
21 the wrong paragraph. Sorry, counsellor.

22 Q. I'm sorry. I was confusing. You don't know what
23 Microtrol is; correct?

24 A. It's a marketing term. I'm not sure what Microtrol
25 is. I'm not sure what it isn't.

Rudnic - cross

1 Q. You are a named inventor on the Adderall patent, U.S.
2 Patent No. 6,322,819. Correct?

3 A. Yes.

4 Q. And that's at DTX-2116.

5 A. Yes.

6 MR. STEUER: I move to admit Exhibit 2116.

7 MS. WILGOOS: No objection, your Honor.

8 THE COURT: It's admitted.

9 (DTX No. 2116 received into evidence.)

10 BY MR. STEUER:

11 Q. And are you also a named inventor on the Carbatrol
12 patents, U.S. patent number 5,326,570, which is the 2326?

13 That's in the back.

14 A. Not in my copy.

15 Q. Okay.

16 A. I'm willing to agree I was the inventor of two
17 Carbatrol patents. If you ask questions about them, I may
18 want a copy.

19 Q. All three of these patents had to do with beadlets
20 within a capsule?

21 A. Yes.

22 Q. And all three of these patents were actually licensed
23 from CollaGenex to Shire; correct?

24 A. No.

25 Q. No?

Rudnic - cross

1 A. No.

2 Q. No? You don't know that?

3 A. All three of these patents were licensed by
4 CollaGenex?

5 Q. No, were licensed to CollaGenex from Shire.

6 A. I don't believe that is the truth.

7 Q. You don't think that is right?

8 A. Well, the rights to use something, I don't know, but
9 I know that these products are being sold by Shire.

10 Q. Okay. I didn't say it was an exclusive license but
11 the use of the patents was licensed to CollaGenex. Are you
12 aware of that?

13 A. No.

14 Q. Okay. Now, you do understand that Shire claimed that
15 your formulations for Carbatrol were examples of Microtrol
16 technology; correct?

17 A. They said that.

18 Q. All right. And Carbatrol uses a mixture of instant
19 release delayed release and sustained release beadlets in a
20 single dose; correct?

21 A. Mostly sustained release, yes.

22 MS. WILGOOS: Your Honor, I'm going to object.

23 This is outside the scope of the report to the extent he is
24 attempting to use it as prior art.

25 THE COURT: Any response, Mr. Steuer?

Rudnic - cross

1 MR. STEUER: It's discussed both in his report
2 and in prior testimony by the experts.

3 THE COURT: I will note the objection for the
4 record. As I said, I'm not going to rule on that objection
5 during the trial. Go ahead.

6 BY MR. STEUER:

7 Q. Adderall, like Oracea, uses a mixture of instant
8 release and delay released beadlets in a single dose;
9 correct?

10 A. Correct.

11 Q. However, for purposes of your opinion, you have
12 assumed that Chang did not use the technology that was used
13 for Carbatrol in the creation of Oracea; correct?

14 A. That's correct.

15 Q. Now, it's your understanding that a publication may
16 anticipate a patent even if the anticipation is not
17 contained within preferred embodiments or examples; correct?

18 A. That's correct.

19 Q. And you understand that the scope of the Ashley
20 patents for anticipation analysis is not limited to any
21 preferred embodiments or examples; correct?

22 A. I understand that. But that is not what I would take
23 away from those patents.

24 Q. In fact, it's your understanding that a publication
25 may anticipate even if it has no examples and no preferred

Rudnic - cross

1 embodiments; correct?

2 A. That's correct.

3 Q. In your testimony, you focus on the embodiments in
4 examples of the Ashley applications to support your
5 conclusion that they do not anticipate; correct?

6 A. That's correct.

7 Q. But just to be correct, the '106 patent that you
8 looked at does not require a gastro-retentive formulation;
9 isn't that correct?

10 A. No, but it's not what the patent is talking about.
11 And one of normal skill in the art would look at that for
12 what it is. A 12 to 24 hour release high up in the GI
13 tract. That is gastro-retentive.

14 Q. In fact, the patent specifically allows any form of
15 oral dosing as well as injectables for that patent?

16 A. Without any examples, without any way of
17 accomplishing what gratuitously is thrown in there. And I
18 think one of normal skill would look at that and discount
19 that and go right to what the center portion of those
20 applications are, which is a gastro-retentive sustained
21 release system, 12 to 24-hour release. That is what they
22 would look at.

23 Q. But the application, the claims in the application
24 are not limited to those concepts at all; isn't that right?

25 A. I believe you are obligated to tell how you are going

Rudnic - cross

1 to accomplish what you say you are going to in these patents
2 but they're not limited.

3 Q. And, in fact, let's take a look at -- I think you had
4 an excerpt in one of your demonstratives. Now, if we could
5 put up 218. PDX-218.

6 And you highlighted the part that says all three
7 release agents?

8 A. Yes.

9 Q. You didn't highlight the first sentence of that
10 paragraph. Why not?

11 A. Because if you read what they're trying to accomplish
12 in this patent, that is what they're really talking to. The
13 sustained release component there is the primary component
14 that would allow them to get the 12 to 24 hour substantially
15 constant release. And instantaneous release, as Ashley says
16 here, or the delayed release that starts in 12 hours does
17 not accomplish that goal.

18 And so I can understand why he might want an
19 instantaneous release to cover the front end of that
20 sustained release, or delayed release to cover the back end,
21 which, had he actually tried to do it, wouldn't have worked.
22 The sustained release is really what he is relying on here.

23 Q. Dr. Rudnic, the patent specifically says in that
24 first sentence, you do not need all three, any combination
25 will suffice to practice the method. Correct?

Rudnic - cross

1 A. I think anyone of normal skill in the art would know
2 that that is not true.

3 Q. So you think that Ashley put a false statement here
4 in his patent application?

5 A. I think it's a naive statement.

6 Q. You talk about your opinions on, briefly your
7 opinions on infringement. Now you, base your opinion that
8 Mylan's ANDA product infringes claims 4 and 18 of the Chang
9 patent on your analysis of the PK data from the pivotal
10 trial; correct?

11 A. That's correct.

12 Q. And your analysis and your expert report was attached
13 as Exhibit C to your report. Correct?

14 A. Correct.

15 Q. Do you remember that?

16 A. Yes.

17 Q. Take a look at Defendant's Exhibit 1305.

18 Dr. Rudnic, 1305 is what you attached to your
19 report; correct?

20 A. That's correct.

21 Q. But today, you have a different chart; right?

22 A. It's highlighted differently but it's the same chart.

23 Q. It's highlighted differently. Let's put that up.

24 It's PDX-209.

25 And why didn't you like your first chart?

Rudnic - cross

1 A. It was too busy.

2 Q. It was too busy. Okay.

3 Now, you understand what we're trying to find
4 out here is whether the people that take this drug are going
5 to have a steady state between .3 and .8 micrograms per
6 milliliter of blood; right?

7 A. That is correct.

8 Q. Okay. And so .3 micrograms is equivalent to 300
9 nanograms; correct?

10 A. That's correct.

11 Q. So it's actually between 300 and 800 nanograms;
12 right?

13 A. Yes. And I think from FDA parlance, that would be
14 anywhere from 250 nanograms to 849 nanograms.

15 Q. Is that what the patent says?

16 A. No, it talks about micrograms.

17 Q. Is that what the Court's construction says?

18 A. I'm not sure what the Court's construction says, but
19 .3 to .8.

20 Q. Did you use the Court's construction of this
21 limitation when you prepared your opinion?

22 A. No.

23 Q. And so looking at your list that you have here,
24 let's look at 209. Steady state is 24 hours; right? Is
25 24 hours -- steady state measures blood levels over a

Rudnic - cross

1 24-hour period; correct?

2 A. You are mixing a couple of terms, but let me try to
3 help you. Steady state measured over the 24 hours of the
4 dosing interval.

5 Q. Okay.

6 A. At steady state.

7 Q. Thank you. Thank you for that correction. So what
8 is here is plotted values of the drug in the blood over
9 24 hours, taken -- the blood is taken at a half hour, an
10 hour, an hour and-a-half and so on; is that correct?

11 A. That's correct.

12 Q. What we see here, and this is basically a ratio that
13 is being measured here; right?

14 A. That's correct.

15 Q. And you are assuming the Mylan ANDA product will have
16 the same characteristics?

17 A. Well, the FDA assumes that or they wouldn't approve a
18 fed and fasted bio-state.

19 Q. That's what you believe as well?

20 A. I agree with the FDA.

21 Q. Okay. So if you look at the last column here, right
22 before the next dosing period, it turns out there is only
23 one of the 31 patients that actually fall within that .3 to
24 .8 range, isn't there?

25 A. No, there is three.

Rudnic - cross

1 Q. Okay. So which three would those be?

2 A. It would be subject 5, subject 18, and subject 20.

3 Q. So your opinion that numbers 5 and 18 falls in the
4 range is that 281 nanometers and 284 -- excuse me --
5 nanograms and 284 nanograms are between .3 micrograms and
6 .8 micrograms?

7 A. Yes, because .281 is .3 as per the FDA.

8 Q. Okay. And --

9 A. Blood level data is at one decimal point for the FDA.
10 This is 0.3.

11 Q. But if I'm just trying to figure out if something is
12 between the goal posts, 281 is less than 300; right?

13 A. No.

14 Q. Okay. 281 is between 300 and 800?

15 A. .281 -- 281 is the same as 0.3.

16 Q. Okay.

17 A. You are moving the goal post because the goal posts
18 are .3 to .8.

19 Q. Okay.

20 A. Not 300 to 800.

21 Q. The patent doesn't say about .3 or about .8?

22 A. It says .3 to .8.

23 Q. And the only one that I will say is actually above
24 300 nanograms is, I might contend on this chart, is patient
25 20; correct?

Rudnic - cross

1 A. Well, you are contending it.

2 Q. Well, you would agree that the blood level at hour 24
3 is over 24 -- is over 300 nanograms; right?

4 A. Is over 300 nanograms, correct.

5 Q. Is over by one nanogram; right?

6 A. It's over.

7 Q. And that is a billionth of a gram; correct?

8 A. Over is over.

9 Q. Okay. So of these 31 people, suppose we're limiting
10 ourselves to numbers that are between .3 to .8. We have one
11 out of 31 and that person squeaks in by a nanogram; right?

12 A. No, you have three. 0.3 to 0.8, you have three as
13 per the FDA rounding criteria. And you have got three:
14 subject 5, subject 18 and subject 20 all make it. And as
15 the FDA says, if it hits the goal posts and goes in, it's
16 in.

17 Q. Okay. Let's go back to PDX-218, if we could. With
18 respect to that Figure 1, that's from the Ashley
19 application. Correct?

20 A. Hang on, counselor. It's on the screen here, if that
21 helps. It should be right in front of you.

22 Q. What was the number of the document?

23 A. It was Demonstrative 218.

24 Q. Okay.

25 A. Okay.

Rudnic - cross

1 Q. And I believe what you testified was that this was
2 Ashley's depiction of a release profile where the
3 tetracycline compound of the formulation is released over an
4 approximately 16-hour period. Right?

5 A. 12 to 24-hour period.

6 Q. And do you believe that Ashley intended these curves
7 to represent the curves of a single formulation?

8 A. It's hard to imagine what he was imagining. But I
9 think one of normal skill would look at this and say he was
10 largely relying on the sustained release portion. Whether
11 he was relying on the immediate release or the delayed
12 release as some helping at that time the front and back end
13 of this curve, I couldn't tell you. But I think one of
14 normal skill looking at this would say this is a sustained
15 release product.

16 Q. And you are aware that the inventor Robert Ashley did
17 not intend that to represent the release profile of a single
18 drug. Correct?

19 A. I don't know what Ronald Ashley intended.

20 Q. Did you read his deposition?

21 A. No.

22 Q. So you don't know what he said about it?

23 A. No.

24 Q. You didn't think that would be useful in deciding
25 whether or not his application anticipated the Chang

Rudnic - cross

1 invention?

2 A. It might have. I just didn't read it.

3 Q. Didn't you testify repeatedly as to what Ashley
4 testified to on your direct exam?

5 A. I am aware that Ashley admitted that he had no
6 formulation expertise. And I saw that portion of his
7 deposition.

8 Q. So did somebody tell you that or did you actually
9 read the deposition?

10 A. I read that portion of the deposition.

11 Q. Why did you decide to read that portion of the
12 deposition?

13 A. Because the rest of it was rather long.

14 Q. Didn't have time for it, maybe?

15 A. No, I had time for it. It just didn't seem relevant.

16 MR. STEUER: Okay. I think that's enough.

17 Thanks, Your Honor.

18 THE COURT: Any redirect?

19 MS. WILLGOOS: Briefly.

20 REDIRECT EXAMINATION

21 BY MS. WILLGOOS:

22 Q. I guess we will start with infringement, since that's
23 where we seem to have left off.

24 MS. WILLGOOS: May I approach the witness, Your
25 Honor?

Rudnic - redirect

1 THE COURT: You may.

2 BY MS. WILLGOOS:

3 Q. I have just given you a copy of your expert report to
4 refresh your recollection. Could you please turn to Page
5 64?

6 MR. STEUER: Shouldn't there be a foundation
7 laid that he needs his recollection refreshed?

8 THE COURT: Where are we going?

9 BY MS. WILLGOOS:

10 Q. Is that the expert report you set forth in this
11 action, Doctor?

12 A. Yes.

13 Q. Do you recall Mr. Steuer's question as to whether or
14 not you reviewed the claim construction order that the Court
15 set forth regarding the Chang patent in this case?

16 A. Yes.

17 Q. If you could turn to Paragraph 64 of your report?

18 THE COURT: I am not sure why you are directing
19 him to his report. The objection is sustained.

20 MS. WILLGOOS: Thank you, Your Honor.

21 BY MS. WILLGOOS:

22 Q. You can set that aside, Dr. Rudnic.

23 Do you recall whether or not you reviewed the
24 claim construction order in this case?

25 A. I did.

Rudnic - redirect

1 Q. And do you recall the definition of the claim
2 construction of between 0.3 to 0.8 micrograms per
3 milliliter?

4 A. I do.

5 Q. Do you recall anything in that deposition that
6 discussed nanograms per milliliter?

7 A. No.

8 Q. Do you recall any portion of that deposition that
9 discussed whether or not it was appropriate to round in
10 deciding what met that claim limitation?

11 A. No.

12 Q. Is it your opinion that patients need to have steady
13 state blood levels at all time points in order to infringe
14 the claims, Claims 4 and 18 of the Chang patent?

15 MR. STEUER: Objection, Your Honor. The Court
16 has already ruled on this.

17 THE COURT: Overruled. You can answer the
18 question.

19 THE WITNESS: It's my opinion that they are not.

20 BY MS. WILLGOOS:

21 Q. Now, earlier in the beginning portion of the exam,
22 Mr. Steuer asked you if you were aware of prior art of 100
23 milligrams doxycycline that was administered once daily. Do
24 you recall that testimony?

25 A. Yes.

Rudnic - redirect

1 Q. Are you aware of any immediate release formulation of
2 100 milligrams that meets a steady state claim limitation of
3 0.1 to 1.0 micrograms per milliliter as a minimum maximum?

4 A. No.

5 Q. Are you aware of any 100 milligram once-daily
6 formulations that meet a steady state claim limitation of
7 between 0.3 and 0.8 micrograms per milliliter?

8 A. No.

9 Q. Now, Mr. Steuer had asked you a question regarding
10 whether knowing the pH or the change in the pH would lead
11 one to believe there was an absorption window in
12 doxycycline. And you had responded that you thought
13 Faulding proved that false, but were not able to finish
14 answering the question. I just wanted to get your opinions
15 on that point, Dr. Rudnic.

16 A. Well, an absorption window is not necessarily
17 dependent on the pH of the intestinal tract. Those are two
18 completely independent things.

19 A lot of antibiotics work because they look like
20 peptides. They look like food to bacteria. You take them
21 in and metabolically bring them in.

22 So they look like a peptide. Well, there are
23 peptide transporters in the intestine, PEP T-1 and MRNase
24 are two of them that are particularly amenable to antibiotic
25 transport. They have nothing to do with pH. And they have

Rudnic - redirect

1 nothing to do with any of the other kinds of limitations of
2 ionization or some of the things that Faulding was trying to
3 accomplish.

4 So since Faulding, their approach was to create
5 an acidic microenvironment for the drug. Because that
6 failed, it tells that you pH and ionization wasn't the
7 problem.

8 Q. Now, with respect to those Faulding formulations, do
9 you believe that any of them would have been clinically
10 acceptable?

11 A. None of them would have been.

12 Q. Why is that?

13 A. Well, first of all the FDA would never have approved
14 any of them because they would have had a very low
15 absorption, which would have given drug into the lower GI
16 tract, which causes long-term gastric and colonics problems.
17 It is an unsafe product.

18 Q. Would a composition with only 50 percent absorption
19 as an oral formulation once daily product of doxycycline be
20 satisfactory as a copy of the Chang patent?

21 A. No.

22 MS. WILLGOOS: Thank you, Dr. Rudnic. I have no
23 further questions.

24 THE COURT: Thank you, Doctor. You can step
25 down.

Rudnic - redirect

1 (Witness excused.)

2 THE COURT: You can call your next witness.

3 MS. WILLGOOS: Dr. Matthew Grisham, Your Honor
4 is the plaintiffs' next witness.

5 THE COURT: Okay. Fine.

6 MATTHEW B. GRISHAM, having been duly
7 sworn as a witness, was examined and testified as
8 follows ...

9 THE COURT: Good afternoon, Dr. Grisham.

10 MS. WILLGOOS: May I approach the witness, Your
11 Honor?

12 THE COURT: You may. You may proceed.

13 MS. WILLGOOS: Thank you.

14 DIRECT EXAMINATION

15 BY MS. WILLGOOS:

16 Q. Good afternoon, Dr. Grisham.

17 Can you please introduce yourself to the Court?

18 A. Yes. My name is Matthew Grisham. I am a Boyd
19 Professor at Louisiana State University Health Sciences
20 Center in Shreveport, Louisiana.

21 Q. What is a Boyd Professor?

22 A. A Boyd Professor is the highest rank that can be
23 bestowed in the multi-institutional Louisiana State
24 University system.

25 Q. What department are you affiliated with at the

Grisham - direct

1 university?

2 A. I am in the Department of Molecular and Cellular
3 Physiology.

4 Q. Can you briefly describe your educational background
5 for the Court?

6 A. Yes. I received my Ph.D. in biochemistry at Texas
7 Tech University Health Sciences Center, following thereafter
8 a postdoctoral fellowship at St. Jude's Children's Research
9 Hospital in Memphis, where I studied immunology and
10 inflammation.

11 Q. And do you have a particular area of research
12 interest?

13 A. Yes. My research interests are in acute and chronic
14 inflammation, with a particular focus on reactive oxygen and
15 nitrogen metabolites, such as nitric oxide.

16 Q. Have you authored any papers related to nitric oxide?

17 A. Yes, I have. I have authored several papers on the
18 pathophysiologic role of nitric oxide in inflammation.

19 Q. Have you served on any editorial boards of any
20 journals?

21 A. Yes. I served as an associate editor on the Journal
22 for Free Radical Biology in Medicine and I am serving as
23 associate editor on the American Journal of Physiology, and
24 I serve on editorial boards for a variety of other journals.

25 Q. Are you a member of any professional societies?

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1 A. Yes. I am a member of the American Association of
2 Immunology, the Society of Mucosal Immunology, the Society
3 for Free Radical Biology and Medicine, the American
4 Gastrointestinal Association.

5 Q. Dr. Grisham, can you please turn in your witness
6 binder to PTX-245.

7 A. Yes.

8 Q. Can you tell me what that is?

9 A. That is a copy of my current curriculum vitae.

10 Q. Does it fairly and accurately summarize your
11 educational and professional experience?

12 A. Yes, it does.

13 MS. WILLGOOS: Your Honor, we would like to move
14 PTX-245 into evidence.

15 MR. REED: No objection.

16 THE COURT: It is admitted.

17 (Plaintiffs' Trial Exhibit No. 245 received in
18 evidence.)

19 MS. WILLGOOS: We would like to tender Dr.
20 Grisham as an expert in molecular and cellular physiology
21 particularly as it relates to the biological functions of
22 nitric oxide.

23 THE COURT: Any objection?

24 MR. REED: None.

25 THE COURT: He is so recognized.

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1 BY MS. WILLGOOS:

2 Q. Dr. Grisham, can you please describe for me how you
3 prepared the demonstratives that you will be using in your
4 testimony today?

5 A. Yes. I prepared these after a critical review of the
6 published scientific literature in collaboration with
7 counsel.

8 Q. Can you please turn to PTX-3 in your witness binder,
9 and PTX-4 as well, if you could review those for me.

10 A. Yes.

11 Q. What are those documents?

12 A. Those are the Amin patents '395 and the Amin patent
13 '775.

14 Q. And did you review those patents in forming your
15 opinions today?

16 A. Yes, I did.

17 MS. WILLGOOS: Your Honor, at this time Galderma
18 would like to move into evidence PTX-3 and PTX-4, a copy of
19 the two Amin patents.

20 MR. REED: No objection.

21 THE COURT: They are admitted.

22 (Defendants' Trial Exhibits Nos. 3 and 4
23 received in evidence.)

24 BY MS. WILLGOOS:

25 Q. Have you formed any opinions regarding the Amin

Grisham - direct

1 patents?

2 A. Yes, I have.

3 Q. Can you summarize for us your opinions regarding
4 those patents?

5 A. I believe that Mylan's generic product infringes on
6 Claims 1, 2, 4, 11, 13, 14 and 16 of the Amin '395 patent.
7 I also believe that Mylan's generic product infringes on
8 Claims 1, 2, 4, 5 and 9 of the Amin '775 patent.

9 Q. Have you also formed opinions regarding whether
10 Galderma's drug Oracea is covered by the Amin patents?

11 A. Yes, the use of Oracea is covered by the Amin
12 patents.

13 Q. Generally speaking, what have you relied on in
14 forming your opinions?

15 A. I have relied on the patents themselves, and I have
16 relied on the -- Mylan's package insert, as well as reviewed
17 the published literature.

18 Q. Can we please turn to the next slide, 302. Dr.
19 Grisham, can you describe for us what nitric oxide is?

20 A. Yes. Nitric oxide is a signaling molecule that
21 possesses a diverse range of biological functions in many
22 different cell types.

23 It mediates the relaxation of blood vessels,
24 promoting vasodilation. It is involved in host defense and
25 immunity. And it also modulates the inflammatory responses.

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1 In particular, leukocytes, such as neutrophils and
2 macrophages, are major producers of nitric oxide during
3 inflammation.

4 Q. How is nitric oxide produced?

5 A. Nitric oxide is produced by a family of enzymes
6 termed nitric oxide synthase, NOS.

7 Q. Can we turn to the next Slide, 303, please. What
8 forms of NOS exist?

9 A. There are two types of nitric oxide synthase.

10 There is the constituent form of NOS. This is
11 always turned on. It produces very low and continuous
12 levels of nitric oxide that have been shown to be intimately
13 involved in normal vascular, cardiovascular function. It's
14 also been well-documented that cNOS derived nitric oxide is
15 anti-inflammatory in nature.

16 Q. And what is iNOS?

17 A. INOS is normally not expressed, is not present.
18 However, during the genesis of inflammation, mediators
19 induce the expression of iNOS in a variety of different
20 cells, especially the leukocytes, very high levels.

21 Sustained overproduction of NO can take place, and the
22 literature tells us that this sustained overproduction of
23 nitric oxide by iNOS is pro-inflammatory in nature.

24 Q. Let's turn to the next slide. Can you explain for us
25 what inflammation is?

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1 A. Yes. Inflammation is a physiologic and protective
2 response to fight infection and to repair tissue injury.

3 It is characterized by increases in blood flow
4 in the influx of white blood cells that make their way out
5 into the tissue, where they fight infection and they repair
6 injured tissue.

7 Q. What is chronic inflammation?

8 A. Chronic inflammation results from a dysregulated
9 immune response that overruns normal mechanisms. Chronic
10 inflammation, chronic inflammation is associated with the
11 up-regulation of iNOS and the overproduction of nitric
12 oxide.

13 This leads to pathogenic changes within the
14 chronically inflamed tissue.

15 Q. What do you mean by a dysregulated immune response?

16 A. This is an immune response that takes place that's
17 not normally regulated and therefore there is no governor on
18 the inflammatory response and it can then proceed for, in
19 some cases weeks, months, or years.

20 Q. Dr. Grisham, I would like you to turn to Tab PTX-333
21 in your witness binder. Can you tell me what this document
22 is?

23 A. Yes. This is a review article by Clancy and Abramson
24 entitled Nitric oxide - A Novel Mediator With Inflammation.

25 Q. Can you turn to -- have you reviewed this article in

Grisham - direct

1 forming your opinions?

2 A. Yes, I have.

3 Q. And can you also turn to Tab PTX-317 in your witness
4 binder?

5 A. Yes.

6 Q. And what is this article?

7 A. This is a published report by Amin and coworkers
8 entitled A Novel Mechanism of Action of Tetracyclines,
9 Effects on Nitrous Oxide Synthase.

10 Q. And have you reviewed this article as well in forming
11 your opinion?

12 A. Yes, I have.

13 MS. WILGOOS: Your Honor, at this time, Galderma
14 would like to move into evidence PTX-333 and PTX-317.

15 MR. REED: No objection.

16 THE COURT: They are admitted.

17 MS. WILGOOS: Thank you.

18 BY MS. WILGOOS:

19 Q. What conclusion did this article reach regarding
20 nitric oxide?

21 A. Could you repeat the question, please?

22 Q. Sure. What did you learn from these articles?

23 A. Excuse me. I have learned that nitric oxide is an
24 important pathophysiologic mediator in chronic inflammation.
25 The excessive production of nitric oxide is intimately

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1 linked to the pathogenetic changes that one observes in
2 inflamed tissue.

3 Q. Does nitric oxide have any effects in the skin?

4 A. Yes. Nitric oxide has been shown in a few studies to
5 produce some of the changes that we see, especially in
6 psoriatic lesions, chronic inflammation of the skin -- it
7 promotes the regulation of iNOS in skin cells and skin
8 tissue. It results in vasodilation. Vascular leakage
9 results in tissue swelling, leucocyte invasion, and new
10 vessel growth. This is called the angiogenesis.

11 Q. What have you relied on in forming your opinions
12 regarding the effects of nitric oxide in the skin?

13 A. I relied on the published scientific literature for
14 this.

15 Q. Can you please turn to PTX-328? And let me know what
16 that document is.

17 A. Yes. This is a paper by Bruch Gerhars and coworkers
18 entitled, A Proinflammatory Activity of Interleukinase in
19 Human Skin, Expression of the Inducible Nitric Oxide
20 Synthase With Psoriatic Lesions in Cultured Keratin Cites.

21 Q. And can you turn to PTX-329 and describe that
22 document for us.

23 A. Yes. This is a paper by Bruch-Gerharz and coworkers,
24 a review article entitled: Nitric Oxide and Its
25 Implications in Skin Homeostasis and Disease. This is a

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1 review article.

2 Q. Can you please turn to PTX-330. And let us know what
3 that document is.

4 A. This is another article by Bruch Gerhars and
5 coworkers entitled Nitric Oxide in Human Skin, Current
6 Status and Future Prospects.

7 Q. And have you reviewed each of these documents in
8 forming your opinions regarding the Amin patents?

9 A. Yes, I have.

10 MS. WILGOOS: Your Honor, at this time Galderma
11 would like to move into evidence PTX-328, PTX-329, PTX-330.

12 MR. REED: No objection.

13 THE COURT: They are admitted.

14 MS. WILGOOS: Thank you.

15 (PTX Nos. 328, 329, 330 received into evidence.)

16 MS. WILGOOS: Can we turn to the next slide,
17 please.

18 BY MS. WILGOOS:

19 Q. What do these three articles say about the affects of
20 nitric oxide in the skin?

21 A. These three articles tell us that nitric oxide is an
22 important pathogenic mechanism -- pathogenic mediator of the
23 inflammation that you observe in skin diseases, especially
24 skin diseases such as psoriasis.

25 These also, these articles also tell us that

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1 nitric oxide is directly linked with the characteristic
2 neutrophil, leukocyte infiltration into these tissues.

3 Q. Dr. Grisham, do you have an understanding of rosacea?

4 A. Yes, I do.

5 Q. What is your understanding?

6 A. My understanding, and it's clear based on clear
7 evidence from the literature, that this is a chronic
8 inflammatory skin disorder.

9 Q. What are the characteristics of the disorder?

10 A. There is swelling, hyperemia, erythema, the reddening
11 of the face, of the formation of pustules and papules. As
12 we heard earlier this morning, these are essentially pimples
13 composed of large numbers of inflammatory leukocytes such as
14 neutrophils and macrophages.

15 Q. Can you please turn in your witness binder to
16 PTX-361?

17 A. Yes.

18 Q. What is this document?

19 A. This is a document by Korting and Schollmann, and it's
20 entitled Tetracycline Actions Relevant to Rosacea Treatment.

21 Q. Okay. Can you please turn to PTX-422, and tell us
22 what this document is?

23 A. Yes. This is a published review article by Yamasaki
24 and Gallo entitled, Molecular Pathology of Rosacea.

25 Q. Have you reviewed each of these articles in forming

Grisham - direct

1 your opinions?

2 A. Yes, I have.

3 Q. Let's turn to your next slide please, 309.

4 What do these articles say about rosacea?

5 A. That rosacea is, in fact, an inflammatory disease.

6 It also talks, tells us that to the best of our knowledge,

7 currently rosacea results from an altered or, as I would

8 say, a dysregulated immune response and that the

9 pathogenesis, the signs and symptoms of rosacea are

10 characteristic of a chronic and unregulated inflammatory

11 response.

12 Q. What cell types are involved in rosacea?

13 A. As we heard this morning from Dr. Webster, there
14 appears to be or there is a mixed leukocyte and neutrophil
15 accumulation within not only the tissue but in the pustules
16 and papules. So what this simply means is there are large
17 numbers of these inflammatory leukocytes within the skin and
18 contribute to the formation of the pustules and papules.

19 Q. Can you please turn in your witness binder to
20 PTX-368.

21 A. Yes.

22 Q. And did you review that document in forming your
23 opinions?

24 A. Yes, I did.

25 Q. And what is it?

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1 A. This is a paper by McAleer and Powell entitled, The
2 Pathophysiology of Rosacea.

3 Q. And can you please take a look at PTX-372, and tell
4 us what that document is?

5 A. This is a published review article by Dr. Millikan
6 entitled: Proposed Inflammatory Pathophysiology of Rosacea,
7 Implications For Treatment.

8 Q. Did you review each of these articles in forming your
9 opinions?

10 A. Yes, I did.

11 MS. WILGOOS: Your Honor, at this time,
12 plaintiffs would like to move PTX-372 into evidence.

13 THE COURT: Any objection?

14 MR. REED: None.

15 THE COURT: It is admitted.

16 MS. WILGOOS: Thank you.

17 (PTX No. 372 received into evidence.)

18 BY MS. WILGOOS:

19 Q. Let's turn to your next slide. What do these
20 articles have to say about the cell types that are involved
21 in rosacea?

22 A. What these articles tell us is that rosacea --
23 chronic inflammation of the skin associated with rosacea is
24 associated with the infiltration of large numbers of
25 inflammatory cells such as neutrophils. They also are

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1 important, these inflammatory cells are important for the
2 development of the papules and pustules, and they play key
3 pathophysiologic roles in the development of rosacea,
4 specifically in the form of the pustules and papules.

5 Q. What is the role of nitric oxide and iNOS in rosacea?

6 A. The regulation of iNOS and the sustained production
7 of nitric oxide are very important in the pathophysiology of
8 rosacea because nitric oxide, as I mentioned, is a potent
9 vasodilator. It also will promote vascular permeability,
10 tissue swelling, visible vessel growth within the face
11 erythema. It will also promote leukocyte recruitment from
12 the circulation, from the blood vessels into the tissue,
13 ultimately resulting in the formation of the pustules and
14 papules. So nitric oxide, overproduction of nitric oxide
15 can produce all of the signs and symptoms of patients
16 suffering from rosacea.

17 Q. Thank you. Can you please turn to PTX-386 in your
18 witness binder?

19 A. Yes.

20 Q. And what is this document?

21 A. This is a manuscript by Rowe and coworkers entitled,
22 constituent endothelial and inducible nitric oxide synthase
23 in inflammatory dermatoses.

24 Q. Can you please turn to PTX-381.

25 A. Yes.

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1 Q. And what is this document?

2 A. This is a document by Perlmutter, et al. It's a new
3 therapy update entitled, Oracea Doxycycline Monohydrate.

4 Q. Have you reviewed each of these documents in forming
5 your opinions regarding the Amin patents?

6 A. Yes, I have.

7 MS. WILGOOS: Your Honor, at this time Galderma
8 would like to move into evidence PTX-386 and PTX-381.

9 MR. REED: No objection.

10 THE COURT: They are admitted.

11 (PTX Nos. 386 and 381 received into evidence.)

12 MS. WILGOOS: Thank you, your Honor.

13 BY MS. WILGOOS:

14 Q. Can we please turn to the next slide.

15 What do these articles tell us about nitric
16 oxide and rosacea?

17 A. As I mentioned, these articles tell us that nitric
18 oxide is intimately involved in the pathophysiology of
19 rosacea. Again, NO is well known to promote the vascular
20 changes associated with rosacea. As I have mentioned,
21 regarding the redness, the swelling, erythema, the visible
22 vessel growth. It's also very important in promoting the
23 extravasation, the infiltration of inflammatory cells from
24 the blood into the tissue and ultimately important for the
25 formation of the pustules and papules. Neutrophils play a

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1 key role in this process.

2 Q. Let's turn to your next slide.

3 Can you explain for us how the symptoms of
4 rosacea arise?

5 A. Yes. This slide shows how the signs and symptoms can
6 arise in a patient with rosacea. As I said early on, early
7 on with the dysregulated immune response, within the dermis,
8 within the tissue, there is the induction of iNOS. This is
9 the case for virtually all chronic inflammatory diseases.
10 There is the sustained over production of nitric oxide which
11 can then produce a variety of different pathophysiologic
12 changes such as the vasodilation, enhanced blood flow,
13 increased permeability which would result in increased
14 swelling as well as new vessel growth, angiogenesis, and
15 importantly will promote the invasion of inflammatory
16 leukocytes such as neutrophils. All four of those
17 pathophysiologic events can contribute directly to the signs
18 and symptoms of rosacea.

19 Q. Okay. Thank you. Let's turn to your next slide.

20 And can you just talk us through what you set
21 out for us here?

22 A. Yes. This is a very brief video showing sort of a
23 miniature time lapse of the development of rosacea. As
24 you can see here, this is a normal dermis. This is
25 someone who does not suffer or is not about to suffer from

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1 rosacea. As you can see, all of the leukocytes, which is
2 the neutrophils, are located within the blood vessels.
3 Tissue, normal tissue is known to have several of these
4 tissue-derived macrophages that are there presently.

5 During the induction of disease, these
6 neutrophils are recruited out of the circulation and into
7 the tissue where these mediators induce the upregulation of
8 iNOS within the neutrophils as well as the macrophages,
9 thereby producing very large amounts unregulated amounts of
10 nitric oxide that can impinge upon the blood vessels there
11 by causing a swelling of those blood vessels, vasodilation,
12 vascular leakage, swelling; and, in addition, the nitric
13 oxide acts to promote the recruitment of these inflammatory
14 neutrophils in large numbers out of the vessels into the
15 tissue, ultimately resulting in a collection or collections
16 of these inflammatory cells, these iNOS producing
17 inflammatory cells into the formation of the pustules --
18 papules and pustules.

19 And the net sum or the sum of all of these
20 actions is the appearance of the reddening, the swelling,
21 the erythema and the formation of these pimple-like
22 structures, papules and pustules.

23 Q. Thank you, Dr. Grisham.

24 Let's switch topics and talk specifically about
25 the Amin patents themselves.

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1 What is your understanding of the invention of
2 the Amin patent?

3 A. The Amin patents describe the use of tetracycline
4 compounds to inhibit nitric oxide production, and they also
5 describe the use of tetracycline compounds to inhibit the
6 expression of the iNOS enzyme.

7 Q. How does tetracycline compounds work to inhibit iNOS?

8 A. They inhibit, very interestingly, the expression of
9 the -- of the enzyme.

10 Q. Let's turn to the next slide.

11 At the time the Amin patents were filed, what
12 inhibitors of nitric oxide synthase or iNOS were known in
13 the art?

14 A. Virtually, all the inhibitors were known at the time
15 of the patent and were readily available to investigators
16 were the L-arginine analogs which inhibited both the
17 constitutive form of NOS as well as the inducible form of
18 NOS.

19 Q. In your opinion, were there any limitations to those
20 inhibitors?

21 A. Yes. It was unfortunate, and probably this is what
22 has led to a lot of confusion in the literature over the
23 years is the inhibitors, by inhibiting the constitutive form
24 of NOS, actually inhibited normal cardiovascular function.
25 As I mentioned, cNOS derived NO is absolutely critical for

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1 normal homeostatic function in the vasculature. So we were
2 stuck with non-selective or non-specific inhibitors at that
3 time.

4 Q. Let's turn to your next slide, PDX-318.

5 And what have you set out for us on this slide?

6 A. On this slide, I wanted to show the excitement that
7 was generated with the realization that the Amin -- that the
8 tetracycline compounds could selectively prevent the
9 expression of iNOS, thereby inhibiting the overproduction,
10 pathophysiologic production of nitric oxide but sparing
11 constitutive amounts, thereby allowing normal function.

12 Q. Okay. Dr. Grisham in your opinion, does tetracycline
13 have any affect in rosacea?

14 A. Excuse me. Yes, I think it's well accepted that
15 tetracycline attenuates the signs and symptoms of rosacea,
16 especially treats the pustules and papules.

17 Q. What is your opinion based on?

18 A. My opinion is based on the clinical studies that were
19 described earlier in the day and reported in the Mylan
20 package insert.

21 Q. Okay. And let's turn to our next slide.

22 What have you set out for us here?

23 A. This is a slide that describes how tetracyclines can
24 inhibit the formation of pustules and papules as well as the
25 other signs and symptoms of rosacea by inhibiting the up

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1 regulation of iNOS and the overproduction of nitric oxide by
2 fully expressed iNOS.

3 Q. Can you please turn to tab DTX-2091 in your witness
4 binder?

5 A. Let me get this.

6 Yes.

7 Q. What is that document?

8 A. This is the Mylan product insert.

9 Q. Okay. And did you review this document in forming
10 your opinion?

11 A. Yes, I did.

12 Q. And let's take a look at claim 1 of the '395 patent.

13 What is your understanding, Dr. Grisham, of
14 claim 1?

15 A. Claim 1 of the '395 patent describes a method for the
16 use of tetracycline compounds for inhibiting nitric oxide
17 production in vivo.

18 Q. Have you formed any opinion regarding whether Mylan's
19 generic doxycycline product infringes claim 1 of the Amin
20 '395 patent?

21 A. Yes, I have. And I believe that it infringes on
22 claim 1 of the '395 patent.

23 Q. Okay. Let's turn to slide 322. Can you explain for
24 us briefly the basis for your opinion regarding
25 infringement?

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1 A. Yes. The basis of my opinion is based on the Mylan's
2 product label that describes the use of doxycycline at a 40
3 milligram dose which will inhibit the up regulation of iNOS
4 and therefore reduce or inhibit the iNOS production of
5 nitric oxide, which will also decrease the nitric oxide
6 dependent infiltration of inflammatory leukocytes, thereby
7 attenuating or inhibiting the inflammatory lesions such as
8 the pustules and papules.

9 Q. Let's turn to your next slide, which is claim 1 of
10 the '775. What is your understanding of this claim?

11 A. This is a very similar claim in the sense that it
12 describes a method of the use of tetracyclines to inhibit
13 the expression of the enzyme itself, iNOS.

14 Q. And have you formed an opinion regarding whether
15 Mylan's generic product infringes claim 1 of the '775
16 patent?

17 A. Yes. I believe that Mylan's generic product
18 infringes on claim 1 of the '775 patent.

19 Q. Okay. And let's turn to your next slide so you can
20 describe for us the basis of your opinion.

21 A. Yes. The basis of my opinion essentially is as I've
22 just described, and that is that the Mylan generic product
23 uses doxycycline, 40 milligram dose, which will inhibit the
24 upregulation of iNOS, thereby decreasing nitric oxide with a
25 consequent reduction in the recruitment of inflammatory

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1 cells into the dermis and attenuation or the effective
2 treatment for formation of pustules and papules.

3 Q. Let's turn to slide 325.

4 What did you set out for us here?

5 A. On this slide, I wanted to present how doxycycline
6 can prevent the formation of pustules and papules, and it
7 does this by inhibiting the induction of iNOS which results
8 in the consequent reduction of NO production, leukocyte
9 invasion in the formation of these pimple-like lesions.

10 Q. Let's turn to the next claim, claim 11 of the '395
11 patent.

12 Now, do you have an understanding of the claim
13 term that is set out here, a medical condition characterized
14 by excess endogenous production of nitric oxide?

15 A. Yes, I do. The Court defined this term as a disease
16 or condition that results in increased endogenous production
17 of nitric oxide by inducible nitric oxide synthase by cells
18 such as neutrophils and macrophages as well as other cells.

19 Q. Have you formed any opinions regarding whether
20 rosacea is a medical condition as set forth in this claim?

21 A. Yes, rosacea is a chronic inflammatory disease
22 that -- in which iNOS is up regulated.

23 Q. Have you formed an opinion regarding whether Mylan's
24 generic product infringes claim 11 of the '395 patent?

25 A. Yes. I believe that their product infringes on claim

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1 11 of the '395 patent.

2 Q. Okay. Let's turn to your next slide. I think you
3 set that out for us.

4 Can you just briefly describe for us the basis
5 of your opinion?

6 A. Yes. Just very briefly. Mylan's generic product,
7 doxycycline will inhibit the expression of iNOS and nitric
8 oxide production in the chronically inflamed dermis, thereby
9 limiting the infiltration of inflammatory cells in the
10 formation of the pimple-like lesions, the papules and
11 pustules.

12 Q. Let's turn to your next slide, please.

13 What is the drug that is used in Mylan's generic
14 product?

15 A. The drug is doxycycline.

16 Q. How if at all does that inform your opinions
17 regarding infringement of any of the Amin patent claims?

18 A. I believe that Mylan's product infringes on Claims 4
19 and 16 of the '395 patent, as well as Claim 4 of the Amin
20 '775 patent, because doxycycline is being used.

21 Q. Let's turn to Claim 2 of the '395, which we have set
22 out in Slide 329. What is your understanding of Claim 2 of
23 the '395 patent?

24 A. My understanding is that the tetracycline compounds
25 can be used, but have substantially no antimicrobial

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1 activity in vivo.

2 Q. And what definition have you used for your
3 understanding of the claim term that the tetracycline
4 compound has substantially no antimicrobial activity?

5 A. Well, the Court defined this term to say that
6 tetracycline and tetracycline compounds may possess
7 antibacterial activity but they have to be employed at doses
8 or in an amount which has substantially no antibacterial
9 activity.

10 Q. And in your opinion, does Mylan's generic product
11 meet this claim limitation?

12 A. Yes.

13 Q. Let's turn to your next slide, 330. What is --
14 excuse me.

15 Dr. Grisham, can you explain for us the basis of
16 your opinion that Mylan's generic product meets the
17 substantially no antimicrobial activity limitation?

18 A. Repeat that question one more time, please.

19 Q. I was just wondering if you could describe for us the
20 basis of your opinion that Mylan's generic product meets
21 Claim 2?

22 A. Yes. The basis of my opinion is based on Mylan's
23 package insert that states that doxycycline should not be
24 used for treating bacterial infections providing
25 antibacterial prophylaxis or reducing the numbers or

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1 eliminating microorganisms associated with any bacterial
2 disease.

3 Q. How if at all does Mylan's package insert,
4 particularly the portion that you have just recited, impact
5 your opinion regarding infringement of other claims of the
6 Amin patents?

7 A. I believe that the product infringes on Claims 2 and
8 14 of the Amin patent '395, as well as Claim 2 of the '775
9 patent, because these claims state that the tetracycline
10 compounds are -- that are used have substantially no
11 antimicrobial activity.

12 Q. Let's turn to our next claim, Claim 13 of the Amin
13 '395 patent, which is set out on the next slide for us, that
14 requires the medical condition of Claim 5 that we discussed
15 already to be a chronic inflammatory condition.

16 Have you formed an opinion regarding whether
17 Mylan's generic product meets this claim limitation of the
18 Amin patents?

19 A. Yes, I have. And I believe that it does.

20 Q. What is the basis of your opinion?

21 A. Well, it's well known now that chronic -- that
22 rosacea is in fact chronic inflammatory skin disease.

23 Q. Okay. Let's next turn to Claims 5 and 9 of the '775
24 patent, which are set out on Slide 332. What is your
25 understanding of Claim 5 of the Amin '775 patent?

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1 A. It's similar to what we have addressed before. This
2 describes a method for the use of tetracycline compounds in
3 a condition characterized by increased nitric oxide
4 production, such as chronic inflammation.

5 Q. Can you set forth for us your understanding of Claim
6 9 of the Amin '775 patent?

7 A. 9 tells us -- describes the method where tetracycline
8 compounds can be used to treat conditions characterized by
9 abnormally high levels of the inducible form of nitric oxide
10 synthase.

11 Q. Have you formed any opinion regarding whether rosacea
12 is a condition that's described in Claims 5 or 9 of the Amin
13 patent?

14 A. Yes, I have. Rosacea is a chronic inflammatory
15 disease where iNOS is up-regulated and nitric oxide is
16 over-produced, which plays a key mediator in the
17 pathophysiology of the disease.

18 Q. Okay. Have you formed an opinion regarding whether
19 Mylan's generic product infringes Claim 5 of the Amin '775
20 patent?

21 A. Yes. I believe that Mylan's generic product
22 infringes on Claim 5, Claim 5, with the Court's definition
23 describing the increased endogenous production of nitric
24 oxide by inducible NOS, by cells such as neutrophils,
25 macrophages and other cells, those cells that are found in

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1 rosacea patients.

2 Q. And have you formed an opinion regarding whether or
3 not Mylan's generic product meets -- infringes Claim 9 of
4 the Amin '775 patent?

5 A. Yes. I believe, also, that Mylan's product infringes
6 on Claim 9 for many of the same reasons, that rosacea is a
7 chronic inflammatory disease characterized by the increased
8 expression of nitric oxide synthase and the overproduction
9 of nitric oxide by a variety of cells, specifically by the
10 inflammatory neutrophils and macrophages.

11 Q. Let's turn to PTX-334. What documents have you used
12 to form the basis of your opinion regarding infringement of
13 Claims 5 and 9 of the Amin '775 patent?

14 A. I have used Mylan's product insert, as well as the
15 Amin patents. I have used critical evaluation of the
16 published scientific literature.

17 Q. Dr. Grisham, have you formed an opinion regarding
18 whether Mylan will induce or contribute to infringement of
19 the Amin '395 and '775 patents?

20 A. Yes. I believe that they will, in fact, will induce
21 and contribute to the infringement of these patents.

22 Q. Can you explain your opinion for us?

23 A. Yes. Mylan's label instructs doctors and patients
24 how to use Mylan's generic product. By using this product,
25 the up-regulated iNOS and therefore the enhanced production

Grisham - direct

1 of NO will be decreased by the administration of the
2 tetracycline compounds.

3 Q. Let's turn to our next slide and switch topics
4 briefly to talk about Oracea. If you could please turn to
5 PTX-426 in your witness binder, and tell us what this
6 document is?

7 A. This is the -- I am sorry, this is the Oracea
8 product insert.

9 Q. Have you reviewed this document in forming your
10 opinions?

11 A. Yes, I have.

12 Q. And having reviewed that package insert, have you
13 formed an opinion regarding whether Oracea is covered by the
14 claims of the Amin '395 and '775 patents?

15 A. Yes. Oracea is, in fact, covered by the claims of
16 the Amin patents, due to the fact that rosacea is in fact a
17 chronic disease.

18 Q. Can you just explain the basis of your opinion?

19 A. Okay. I thought somebody asked me a question. I am
20 hearing things.

21 Yes. Well, rosacea is in fact a chronic
22 inflammatory disease. It's mediated by the up-regulation of
23 iNOS and the overproduction of NO.

24 40 milligrams of doxycycline will, in fact,
25 treat rosacea and treat the papules and pustules of rosacea

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1 by inhibiting the inducible form of nitric oxide synthase,
2 thereby decreasing the production of the pro-inflammatory
3 mediator, nitric oxide.

4 We also know, it's been well described this
5 morning, the clinical studies demonstrating the clinical
6 efficacy of doxycycline.

7 And last but not least, Oracea and Mylan's
8 generic product are bioequivalent.

9 Q. And just to summarize your opinions for us, Dr. Grisham,
10 do you believe that iNOS is up-regulated in rosacea?

11 A. Yes, I do.

12 Q. Do you believe that -- have you formed an opinion
13 regarding whether the administration of 40 milligrams of
14 doxycycline once daily, as it's formulated in Mylan's
15 generic product, in Oracea, reduces the up-regulation of
16 iNOS in patients with rosacea?

17 A. Yes, I believe that it does.

18 MS. WILLGOOS: Thank you. No further questions.

19 THE COURT: We will take our afternoon break.

20 (Recess taken.)

21 THE COURT: Cross-examination.

22 (Recess taken.)

23 MR. REED: Thank you, Your Honor. Good
24 afternoon. I will pass out binders, if that's all right.

25 THE COURT: That's fine.

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1 CROSS-EXAMINATION

2 BY MR. REED:

3 Q. Good afternoon, Dr. Grisham.

4 A. Good afternoon.

5 Q. I heard what you said during your direct testimony.

6 I have some questions to ask you about things that you said.

7 But I want to first ask you about a couple of things that
8 you did not say.

9 You did not say, for instance, that any test or
10 study has been performed showing a decrease in the amount of
11 endogenous nitric oxide produced when a 40-milligram dose of
12 doxycycline is administered once daily. Right?

13 A. There -- administration of a 40-milligram dose of
14 doxycycline will -- is known to reduce the rosacea, and as a
15 chronic inflammatory disease, iNOS will be up-regulated and
16 it will inhibit the expression of iNOS.

17 Q. Sure. I heard you say that. But I am wondering if
18 you can confirm for me something you did not say. You did
19 not say anything at all about a test or study performed to
20 actually show a decrease in the amount of endogenous nitric
21 oxide produced when a 40-milligram dose of doxycycline is
22 administered once daily. Correct?

23 A. That's correct.

24 Q. You did not say that any test or study has been
25 performed showing the inhibition of endogenous nitric oxide

Grisham - cross

1 production when a 40-milligram dose of doxycycline is
2 administered once daily. Correct?

3 A. There is no -- I did not say that there has been --
4 there is evidence that doxycycline has been shown to reduce
5 nitric oxide production.

6 Q. You didn't say that. Right?

7 A. I did not say that.

8 Q. And you did not say that any test or study has been
9 performed showing the inhibition of iNOS expression when a
10 40-milligram dose of doxycycline is administered once daily.
11 Right?

12 A. It's shown in the patent that doxycycline is very
13 capable of inhibiting both the expression of iNOS and the
14 production of nitric oxide.

15 Q. I appreciate what the patent says. I have read it a
16 few times. If you listen carefully to my question, I think
17 you will be able to say yes or no.

18 You did not say that there has been any test or
19 study and there is not any test or study in the Amin patents
20 showing a 40-milligram daily dose of doxycycline will
21 inhibit iNOS expression. Right?

22 A. You know, the overwhelming amount of literature would
23 tell us that it would inhibit nitric oxide.

24 Q. We are having a little bit of a communication problem
25 here, I think.

Grisham - cross

1 There isn't any study or test or data showing
2 any measurement of inhibition of iNOS expression when a
3 40-milligram dose of doxycycline is administered once a day.
4 Right?

5 A. Not that I am aware of.

6 Q. All of your opinions were more qualitative, not
7 quantitative. Correct?

8 A. Well, my opinions were based on the preponderance of
9 evidence that's in the literature.

10 Q. You didn't give us any numbers. You didn't give us a
11 quantity or an amount of decrease of nitric oxide or iNOS.
12 Correct?

13 A. The evidence that I cited to clearly shows that iNOS
14 is up-regulated and over-produced in a variety of chronic
15 inflammatory diseases and rosacea as we know is one of
16 those.

17 Q. I did hear what you said during your direct
18 examination. And if Ms. Willgoos would like to you repeat
19 it, she is certainly welcome to invite you to do that. But
20 I would like you to very carefully answer the questions that
21 I ask.

22 There is no report demonstrating that a
23 40-milligram daily dose of doxycycline will have any effect,
24 either increasing, decreasing, or no effect at all, on iNOS
25 expression? Yes or no.

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1 A. There is evidence that doxycycline will inhibit NO
2 production in other chronic inflammatory diseases. If you
3 are asking specifically about rosacea --

4 Q. I didn't mention the word rosacea since I have stood
5 up here.

6 I really do think it is going to be helpful for
7 all of us if you will listen very carefully to what I do
8 ask. And what I did ask is the same question that you were
9 asked at your deposition. Do you recall that?

10 A. I believe so, yeah.

11 Q. Do you recall answering that there are no reports
12 demonstrating that 40 milligrams per day of Oracea will have
13 any effect, either increasing, decreasing, or no effect, on
14 iNOS expression? Do you recall that?

15 A. Yes, I believe I made that statement.

16 Q. That's what you testified to. Right?

17 A. Yes.

18 Q. There are no quantitative data showing a decrease of
19 nitrous oxide or an inhibition of iNOS expression. Correct?

20 A. At the 40-milligram dose.

21 Q. Now, in connection with this case, you did not
22 perform any tests or studies to determine whether 40
23 milligrams of doxycycline inhibits iNOS expression or nitric
24 oxide production, did you?

25 A. I have not personally performed tests, no.

Grisham - cross

1 Q. This is true even though you are quite familiar with
2 methods that allow the accurate and sensitive quantification
3 of nitric oxide products and metabolites in multiple
4 biological matrices under normal physiological conditions.

5 Right?

6 A. Correct.

7 Q. In fact, you wrote a paper about that?

8 A. Absolutely.

9 Q. You wrote about the most common methods used, the
10 most practical methods used, to quantify changes in nitric
11 oxide and its metabolites. Right?

12 A. Yes, sir.

13 Q. So you literally wrote the book on how to quantify.
14 And yet in this case you did not perform any test or study
15 to quantify whether this accused product does or does not
16 have any effect at all on nitric oxide or iNOS expression.
17 Correct?

18 A. I personally have not.

19 Q. You are aware of the steady state blood plasma
20 concentration of doxycycline that is provided by a daily
21 dose of Oracea. Right?

22 A. Yes, sir.

23 Q. And that C_{max} is .6 micrograms per milliliter. Right?

24 A. That's my understanding, yes.

25 Q. You are not aware of any scientific literature that

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1 reports that a blood plasma concentration of .6 micrograms
2 per milliliter will decrease the amount of nitrous oxide
3 produced endogenously in a human. Right?

4 A. I think it's a little misleading to talk about the
5 blood levels and whether or not those blood concentrations
6 will inhibit the intracellular expression of iNOS.

7 We are talking about large, potentially large
8 differences in a dose response when performed under
9 physiologic conditions. The data that is normally produced
10 is produced in vitro, in tissue culture cells, with ambient
11 oxygen concentrations, neutral pH. Those are far, far
12 different than an inflamed tissue.

13 Q. I am going to ask that question again, so that I can
14 hear you say yes or no, because I am not exactly sure what
15 you meant by what you just said.

16 We have heard your explanation now. We won't
17 need to hear it again. But I would like to hear yes or no,
18 because I am not sure what your answer is.

19 You are not aware of any studies demonstrating
20 that a dosing with doxycycline to achieve a blood level of
21 .6 micrograms per ml has an effect on nitric oxide
22 production or iNOS expression. Correct?

23 A. Not at those levels, I haven't seen any studies.

24 Q. Such tests could have provided quantitative evidence
25 showing that Mylan's product either does or does not meet

Grisham - cross

1 the requirements set out in the claims of the Amin patents.

2 Right?

3 A. I think the literature would say that it does, in
4 fact, inhibit the expression of iNOS.

5 Q. No literature talks about it. Didn't you just say
6 that there is no literature at that level?

7 A. There is a whole literature on chronic inflammation
8 in other tissues where iNOS is up-regulated. In fact, some
9 of these tetracycline derivatives have been shown, such as
10 in osteoarthritis, to inhibit the production of NO.

11 Q. So you are telling us that the fact that other
12 tetracyclines have --

13 A. Doxycycline in particular.

14 Q. So it is doxycycline, tetracycline as well?

15 A. I don't know.

16 Q. I thought I heard you say tetracycline. But let's
17 limit it to doxycycline at the moment. You are saying that
18 doxycycline at other dosage levels has been shown to inhibit
19 the production of nitric oxide and iNOS expression in
20 chronic inflammatory conditions that are associated with
21 nitric oxide and iNOS expression. Is that right?

22 A. The study that comes to mind is an osteoarthritis
23 study in experimental animals, in dogs, showing that
24 doxycycline administration reduces nitrate and nitrite
25 reduction, which are metabolites of nitric oxide.

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1 Q. And those are at higher levels than what we are
2 talking about in the Oracea product and the Mylan product?

3 A. I cannot remember the dose that was used for the
4 dogs.

5 Q. Okay. Let's talk now about some of the things that
6 you did say in your direct testimony. If we could please
7 put up on the screen PDX-325, I pulled this out of your
8 slides as maybe representative, just because I think it
9 would be helpful for us to talk about your opinion regarding
10 the effect of a 40-milligram dose of doxycycline on iNOS and
11 nitric oxide production. Now, this is, whereas before we
12 were talking about quantitative, this is more qualitative,
13 right, about how it works?

14 A. Yes. This is based on a review of the literature,
15 and on the association or on the induction of nitric oxide
16 in other chronic inflammatory diseases.

17 Q. This doesn't have to do with rosacea?

18 A. Oh, sure, yes. Rosacea is in fact a chronic
19 inflammatory disease.

20 Q. And would it be fair to say that with this slide and
21 through your testimony and your other slides, you described
22 the mechanism of the treatment of papules and pustules of
23 rosacea?

24 A. Yes. This is the mechanism that I described.

25 Q. You were in the courtroom this morning with

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1 Dr. Webster testified, weren't you?

2 A. Yes, I was.

3 Q. You heard Dr. Webster say that we still don't know
4 convincingly what the cause of rosacea is. You heard him
5 say that?

6 A. I believe I remember that.

7 Q. So you disagree with his opinion in that regard; is
8 that right?

9 A. I believe that there is overwhelming evidence in the
10 literature to suggest that this is a pathogenic mechanism
11 involved in the formation of pustules and papules.

12 Q. So he is wrong and you are not wrong?

13 A. I don't believe he is wrong.

14 Q. He just doesn't know?

15 A. No, I believe -- I believe what I'm proposing is
16 correct.

17 Q. But he doesn't believe you. At least you haven't
18 convinced him, right? Because he says we still don't know
19 convincingly what the cause of rosacea is?

20 A. The cause is different than the pathway for the
21 production. No, we don't know what causes it. We know what
22 I'm proposing is what produces papules and pustules.

23 Q. Do you agree with the following statement? The
24 mechanism of action of a 40-milligram dose of doxycycline
25 administered once daily in the treatment of inflammatory

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1 lesions of rosacea is unknown.

2 A. Could you repeat that?

3 Q. Absolutely. The mechanism of action of a
4 40-milligram dose of doxycycline administered once daily in
5 the treatment of inflammatory lesions of rosacea is unknown.
6 Do you agree with that statement or not?

7 A. From what I've seen, from what I've reviewed, I
8 believe there is very good evidence to suggest that a
9 40-milligram dose of doxycycline will inhibit the
10 pathophysiologic generation of nitric oxide, which I believe
11 is a major contributor to papule and pustule formation.

12 Q. So you do disagree with that statement; is that
13 right?

14 A. I don't think you can ever -- I would just restate
15 what I mentioned. And that is on this slide. That
16 tetracycline, I believe its mechanism of action is through
17 the induction, suppression of induction of iNOS.

18 Q. So according to you, the mechanism of action is
19 known, and you disagree with the statement "the mechanism of
20 action of a 40-milligram dose of doxycycline administered
21 once daily in the treatment of inflammatory lesions of
22 rosacea is unknown."

23 A. I would -- I have a hard time disagreeing with the
24 general term of "unknown." We can say that about any
25 disease and yet we have very specific pharmacologic agents

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1 that treat the disease. Is that proof positive? I don't
2 think you can ever be 100 percent sure.

3 Q. So you are not 100 percent sure about your theory or
4 hypothesis regarding the effect of 40 milligrams of
5 doxycycline on rosacea?

6 A. Oh, no. I'm very -- I'm very convinced that this is
7 its mechanism of action.

8 Q. So that means you must disagree with the statement
9 that I've been reading?

10 A. I guess if you force me to say, do I disagree with
11 the statement, I would. But that's a -- it's sort of an
12 oversimplification because that could be used for every
13 single disease known to man.

14 Q. Okay. Well, why don't we take a look at that
15 statement. It's in the Oracea package insert. Did you
16 recognize it as a statement that you ever read before?

17 A. I recognized the statement. I didn't remember it
18 being in the Oracea patent.

19 Q. It's PTX-426, which I believe has already been
20 admitted, on the fifth page of this document, right at the
21 very top.

22 There is a little section there that is entitled
23 Section 12.1, Mechanism of Action. And it says, "The
24 mechanism of action of Oracea in the treatment of
25 inflammatory lesions of rosacea is unknown."

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1 A. Um-hmm.

2 Q. But you think you know it?

3 A. Yes. And the other thing is, correct me if I'm
4 wrong, but I don't think these types of patents, not just
5 the Amin patents ever definitively delineates a mechanism of
6 action when they are put together.

7 Q. I'm not here to testify. I won't try to do that.

8 A. I think this is, this is something that is common to
9 many drug patents, and that was the unique feature of the
10 Amin patents is that it describes a novel mechanism that,
11 until the patent, was completely unknown, completely -- it
12 wasn't even suggested.

13 Q. Okay. Hang on to that thought because I'm going to
14 come back to that in a minute.

15 A. Um-hmm.

16 Q. Are you aware that during the course of trying to get
17 the FDA to approve its product labeling, Galderma actually
18 proposed language that described the mechanism of action and
19 that that proposal was rejected by the FDA? Are you aware
20 of that?

21 A. Yes, I believe I heard discussions regarding that.

22 Yes.

23 Q. And the FDA insisted on the language that we see on
24 the screen, which is that the mechanism of action is
25 unknown; right?

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1 A. Yes.

2 Q. So, in essence, you are telling us that you can
3 explain mechanism of action even though the FDA has not
4 accepted the explanation for the mechanism of action; right?

5 A. I don't --

6 THE COURT: Hold on, doctor. There is an
7 objection.

8 MS. WILGOOS: Yes, I'm going to object. This is
9 beyond the scope of the report.

10 THE COURT: The objection is noted. You can go
11 ahead and answer, doctor, if you have the question.

12 THE WITNESS: Yes. As I said, it's not
13 surprising the FDA rejected that. I believe that --

14 BY MR. REED:

15 Q. My question was whether you were aware of that.

16 THE COURT: Hold on, counsel. He was in the
17 middle of answering your question. Don't interrupt him.

18 MR. REED: Okay.

19 THE COURT: Go ahead, doctor.

20 THE WITNESS: Thank you, your Honor.

21 Yes, I was aware of these discussions. And the
22 answer to your second question is, yes, I believe that this
23 the mechanism of action of doxycycline, of Oracea.

24 BY MR. REED:

25 Q. Let's focus now a little on the '395 patent. I'm

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1 choosing that as a representative patent because the
2 specifications for the two are identical, right, or nearly
3 identical?

4 A. Very similar.

5 Q. They were originally filed together as a single
6 application and then there was a divisional; right?

7 A. Yes.

8 Q. Okay. In the specification -- and this is PTX-3, I
9 think is the number -- the '395 patent, at column 7, lines
10 16 to 21, there is quite a list of conditions for which
11 nitric oxide appears to be involved. Right?

12 A. Yes, sir.

13 Q. The conditions include malaria, senescence, diabetes,
14 vascular stroke, Huntington's disease. If we go down a
15 little bit further, we will see I think it's cardiac --
16 cardiac disease, and, in fact, it also includes juvenile
17 diabetes.

18 These are all medical conditions it lists for
19 which nitric oxide appears to be involved. Right?

20 A. Yes, sir.

21 Q. Rosacea is not in that list, is it?

22 A. It's not in that list but it's one of the chronic
23 inflammatory disorders that would fall into categories
24 consistent with diabetes, with actually cardiovascular
25 occlusive diseases. These are all chronic inflammatory

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1 disorders.

2 Q. If we hop down in this same column and then right up
3 to the top of the next, we'll see another fairly lengthy
4 list of conditions, and I'm not going to try to read all of
5 those. I'm not sure I could pronounce them all.

6 But it says inflammatory conditions treatable by
7 means of the present invention include, for example,
8 osteoarthritis. That is the disease that you mentioned
9 towards the beginning of your testimony where you saw data
10 of studies performed in animals?

11 A. Yes. Where doxycycline was reduced, nitric oxide
12 reduction in the cartilage of these osteoarthritic dogs.

13 Q. The list goes on and on here. It gets all the way
14 down to drug reactions, insect bites, burns, sunburn. Those
15 are all inflammatory conditions treatable by means of the
16 present invention but none of them is rosacea; right?

17 A. No, and I'm sure there is many other chronic
18 inflammatory diseases that are not listed on here as well.

19 Rosacea is, in fact, a chronic inflammatory disease that
20 would be -- would fall under the same category as rheumatoid
21 arthritis, diabetes. It's well known that all of these
22 chronic inflammatory diseases are characterized by the
23 operation of iNOS and overproduction of nitric oxide.

24 Q. And the word "rosacea" does not actually appear
25 anywhere in the entire patent, does it?

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1 A. That doesn't bother me at all.

2 Q. Because your opinion is that every inflammatory
3 disease implicates iNOS; right?

4 A. Virtually all chronic inflammatory diseases have been
5 shown in both humans and experimental animals to have iNOS
6 up regulated, yes. I would stand by that. I wouldn't say
7 every single but virtually all. I haven't seen an
8 immunologically based chronic inflammatory disease when
9 tested, when assessed where iNOS is not up regulated.

10 Q. Okay. Let's talk just for a minute more about the
11 condition rheumatoid arthritis. Now, according to your
12 understanding, iNOS is implicated in the pathogenesis of
13 rheumatoid arthritis; right?

14 THE COURT: Hold on a second.

15 MS. WILGOOS: Objection. It's beyond the scope
16 of the direct. He is asking question about invalidity.
17 Dr. Grisham only opined about infringement.

18 THE COURT: So the objection is it's beyond the
19 scope of the direct.

20 MS. WILGOOS: That's correct.

21 THE COURT: Counsel, any response?

22 MR. REED: Yes. He testified on direct about
23 chronic inflammatory conditions. He identified them,
24 including rheumatoid arthritis.

25 THE COURT: The objection is overruled. You can

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1 go ahead.

2 MR. REED: Thank you, your Honor.

3 BY MR. REED:

4 Q. Now, given what you have described as the mechanism
5 of action for the treatment of rosacea, I'd like to try and
6 quantify things a little bit. If a rheumatoid arthritis
7 patient were given a daily dosage of 200 milligrams of
8 minocycline daily, you would expect these patients would
9 experience a decrease in the production of nitric oxide
10 and/or the expression of iNOS; right?

11 A. Oh, I can't answer that. I would have -- I would
12 have no idea.

13 Q. You did answer it, though, didn't you, at deposition?
14 Do you recall that?

15 A. I don't know if I answered it with 200, with that
16 specificity.

17 Q. Okay. In the binder that I handed to you, the
18 deposition transcript is right there.

19 A. Um-hmm.

20 Q. On page 126 of the transcript, starting at line 15.

21 A. Let's see. 1 --

22 Q. -- 26. 126. Line 15.

23 A. Um-hmm.

24 Q. "Question: Assume today, long after the Amin
25 patent issued, that rheumatoid arthritis patients were given

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1 a daily dosage of 200 milligrams of minocycline; okay?
2 Would you expect that those patients would experience a
3 decrease in the production of NO and/or the expression of
4 iNOS?

5 "Answer: That would be a reasonable
6 prediction."

7 Do you recall giving that answer to that
8 question?

9 A. Well, it's in the transcript so apparently I did.

10 Q. Do you still believe, today, that this dosage of
11 minocycline would cause a decrease in the production of
12 nitric oxide and/or the expression of iNOS in a patient with
13 rheumatoid arthritis?

14 A. I'm just not sure it would. I'm not as -- I just
15 don't know.

16 Q. So you are here to testify about a chronic
17 inflammatory condition, rosacea, that is not listed as one
18 of the conditions treatable by this invention, but you don't
19 know if the treatment of one of the conditions that is
20 listed as being treatable by the invention would actually be
21 treated; is that right?

22 A. Yes. I wouldn't -- my concern is I would want to
23 know how this study would be performed. The preparation
24 of the drug. The administration of the drug. You know,
25 it's just very difficult for me to project now what a

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1 200 milligram per day dose of minocycline, whether it
2 would, under those conditions, have the same effect as
3 40 milligrams. All we know is 40-milligram doses are
4 effective in the treatment of rosacea.

5 Q. I believe that you have testified significantly
6 beyond just the 40 milligrams treats rosacea. I believe you
7 have testified about the mechanism of action and that it
8 inhibits iNOS expression. That that is the mechanism of
9 action. That would be the same mechanism of action if we
10 were talking about a 200-milligram dose of doxycycline,
11 wouldn't it?

12 A. Provided there isn't a bell-shaped dose response
13 curve where the higher you get in dosage, you actually begin
14 to lose efficacy in the dosing of the drug. And this is
15 well known in a variety of other drugs that have been used.

16 Q. Did you look at that, the dosing curve for
17 doxycycline?

18 A. The dosing -- no. I have no experience with in vivo
19 human dosing, so I think it's questionable whether you can
20 extrapolate in a linear fashion on dosing.

21 Q. Okay. What about 200 milligrams of doxycycline
22 daily? What about 100 milligrams of doxycycline daily?
23 Would that decrease the production of nitric oxide and/or
24 the expression of iNOS?

25 A. I think this would have to be a determined in vivo in

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1 a well controlled study.

2 Q. I'm having an awfully hard time understanding how to
3 apply the mechanism of action that you described that would
4 apply to all chronic inflammatory conditions in the event
5 of a 40-milligram dosage of doxycycline but not when you
6 administer 100 milligrams. What difference is there with
7 respect to the qualitative opinion you offered regarding the
8 mechanism of action between the two dosages?

9 A. Without knowing the dose response kinetics, it's
10 virtually impossible to predict how doubling the dose would
11 affect the production or the expression of iNOS and the
12 production of nitric oxide. You would have to do a well
13 controlled in vivo clinical study showing what the dose
14 response is.

15 Q. What about steady state blood concentrations of
16 doxycycline rather than dosages? Do you know what the blood
17 plasma concentration would be of doxycycline if you were to
18 administer 100 milligrams of doxycycline daily?

19 A. I don't know.

20 Q. Would it be higher than the .6 micrograms per
21 milliliter that is achieved by the Oracea product at
22 40 milligrams daily?

23 A. I don't know.

24 Q. You don't know if 40 would be lower than 100?

25 A. I'm not an expert in pharmacokinetics and excretion

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1 of the drug. It's effected by renal clearance of the drug.
2 I don't know.

3 Q. Okay. What about if a patient receives 20 milligrams
4 of doxycycline twice a day for a total of 40 milligrams
5 daily but administered every 12 hours instead of every
6 24 hours? Would that patient experience a decrease in the
7 production of nitric oxide and/or iNOS expression according
8 to your views on the mechanism of action?

9 A. I would believe it would, yes.

10 Q. So a patient receiving 20 milligrams of doxycycline
11 twice per day would experience the reduction of nitric oxide
12 and iNOS expression that is required in all of the asserted
13 claims of the Amin patent. Is that right?

14 A. That dosing of the total of 40 milligram, two
15 20-milligram dosages, showing efficacy in the treatment of
16 rosacea, would have to, in my opinion -- it would have to
17 show an inhibition of iNOS expression in the production of
18 NO, as would a 40-milligram dose.

19 Q. It would have to. Is that what you just said?

20 A. It would indicate that it would.

21 Q. So that would be true if you were here or if you were
22 in Russia. Right? Because it's the same mechanism of
23 action?

24 A. Again, for those kind of extrapolations, you would
25 have to know the patient population. You would have to know

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1 the quality of medical care given. There is a lot of
2 variables that would have to be taken into consideration for
3 that.

4 Q. So the location would change it?

5 A. The quality of medical care in Russia may not be the
6 same as here. The dosing, the composition. Without knowing
7 exactly what was going to be taking place in a controlled
8 clinical study, it would be difficult to extrapolate.

9 Q. I am not talking about a clinical study here. I am
10 talking about giving somebody the pill, the Oracea pill,
11 whether they are in here or in Russia I think there is a
12 difference of whether it is going to affect iNOS, nitric
13 oxide and iNOS expressions?

14 A. Under identical conditions?

15 Q. No. One is in the U.S. one is in Russia. Those are
16 not identical. They are different places.

17 A. It is identical places given exactly the same way, I
18 would say, yes, Oracea would inhibit nitric oxide production
19 in those patients.

20 Q. That would be true whether it was last week or next
21 week as well. Right?

22 A. I would say yes.

23 Q. Or two years ago?

24 A. Yes.

25 Q. Or ten years ago?

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1 A. We start getting back in time and it gets very dicey
2 about making predictions.

3 Q. How is the mechanism of action that you have
4 identified and spent a great deal of time testifying about
5 here different if the exact same administration of
6 doxycycline takes place 20 years ago or today?

7 A. The preparation wasn't even available 20 years ago.

8 Q. So it's the availability of the doxycycline?

9 A. No. It comes down to, you have to compare apples to
10 apples.

11 Q. So let's pretend that --

12 THE COURT: Counsel, he wasn't finished.

13 BY MR. REED:

14 Q. I am sorry.

15 A. You have to compare apples and apples. You start
16 going back and in time and it gets very ticklish on
17 comparing things.

18 There has been no clinical studies that were
19 done before the ones that have been reported here in the
20 courtroom today.

21 I know that Oracea, a 40-milligram dose, will
22 inhibit the expression of iNOS.

23 Q. Periostat, 20 milligrams twice a day a of
24 doxycycline, will do the same thing. Right?

25 A. That would be my belief.

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1 Q. That was Dr. Webster's testimony when he was on the
2 witness stand earlier today. Right?

3 A. Yes.

4 Q. You do agree with that part of his testimony?

5 A. I do.

6 Q. That property, or ability, to reduce nitric oxide and
7 inhibit iNOS expression didn't change before or after the
8 Amin patent inventors recognized it, did it?

9 A. The recognition of the ability of doxycycline to
10 inhibit iNOS expression was never even considered. It was
11 not at the time of the patent. That's why it was granted.

12 Q. It wasn't recognized before the Amin patent inventors
13 recognized it?

14 A. The selective inhibition of expression of iNOS.

15 Q. It wasn't appreciated?

16 A. I don't believe it was known.

17 Q. It was an unknown yet inherent property of
18 doxycycline, wasn't it?

19 A. Amin and his coworkers demonstrated I think fairly
20 clearly especially in the paper that I cited that
21 doxycycline is a selective inhibitor of iNOS and not cNOS.

22 Q. And it wasn't indiscriminately inhibiting before they
23 discovered it selectively inhibits, was it?

24 A. I am not really sure what you are asking.

25 Q. Well, you testified that they discovered that it was

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1 a selective inhibitor. Before they discovered it, it was
2 not an indiscriminate inhibitor. Correct?

3 A. Again, you are going back in time. And nobody that I
4 know investigated it before the Amin and coworker
5 publication and the patent was granted.

6 Q. That just means they were the first ones to recognize
7 it. My question focuses on the property. The property
8 itself didn't change simply because they recognized it, did
9 it?

10 A. You would assume that doxycycline's mechanism of
11 action that I have described would be -- that I described is
12 a characteristic of the doxycycline. But again, no studies
13 were done before the patent to even show whether it had an
14 effect on rosacea.

15 Q. I would like to borrow your animation. To do that I
16 think I have to switch control over to your technician,
17 since we have the slides but not the animation.

18 MR. STEUER: We have it.

19 BY MR. REED:

20 Q. As I understand it, this is a sequence, if I
21 understood the graphics guys right. I am going to ask the
22 sequences to be played one at a time, and I just want to
23 make sure that I understand exactly what you are saying
24 here. Down here along the bottom in this picture, we are
25 seeing a blood vessel. Correct?

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1 A. Yes.

2 Q. Inside that blood vessel we are seeing a neutrophil.

3 Correct?

4 A. Correct.

5 Q. Outside of the blood vessel, in the tissue, is a
6 macrophage. Correct?

7 A. That is correct.

8 Q. Let's move to the animation, please. I believe what
9 we are going to see here is the neutrophil will leave the
10 blood vessel and go out to the tissue, and that once it's
11 out here in the tissue, we are going to see red and blue
12 dots start to appear out of both the macrophage and the
13 neutrophil?

14 A. That's correct.

15 Q. Those right there represent nitric oxide, two atoms
16 in a molecule, one nitrogen, one oxygen. Is that right?

17 A. That's correct.

18 Q. So did you intend to depict, through this animation
19 and this illustration, that neutrophils produce nitric
20 oxide?

21 A. Yes, I did, but produce it in the context of a
22 chronic dysregulated inflammatory response.

23 Q. Do you believe that neutrophils produce nitric oxide?

24 A. Yes, I do, in the context of, like I said, this
25 chronic inflammatory response, where you have the production

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1 of a variety of inflammatory mediators that will inhibit
2 neutrophil apoptosis or self-destruction, thereby allowing
3 it to increase the iNOS expression, as well as in
4 macrophages.

5 MR. REED: Your Honor, I would like to introduce
6 Impeachment Exhibit DTX-3234.

7 THE COURT: Before you do that, let me note for
8 the record the animation that you just examined the witness
9 on was the one associated with PDX-313 through 315.

10 You may proceed with the exhibit you have in
11 hand.

12 MR. REED: Thank you, Your Honor.

13 BY MR. REED:

14 Q. Dr. Grisham, do you recognize Exhibit DTX-2324?

15 A. Yes, I do.

16 Q. It is an article you authored. Right?

17 A. Yes, I sure did.

18 Q. Your name appears right at the end of the list of
19 authors, Matthew P. Grisham?

20 A. I am the senior author, yes.

21 Q. If you look at the bottom of this article, you see
22 the date is November 1995?

23 A. Yes, it is.

24 MR. REED: I offer DTX-2324, Your Honor.

25 THE COURT: Any objection?

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1 MS. WILLGOOS: No objection.

2 THE COURT: It is admitted.

3 (Defendants' Trial Exhibit No. 2324 received in
4 evidence.)

5 BY MR. REED:

6 Q. In this paper, a report is made, following study of
7 polymorpho neutrophils or PMNs. Right?

8 A. Yes, sir.

9 Q. And if we look at the second column, about ten lines
10 down -- the second-to-last sentence here begins, in
11 contrast, reads, In contrast, neither circulating nor
12 extravasated human PMNs contain iNOS messenger protein, or
13 enzymatic activity?

14 Did I read that right?

15 A. That's correct.

16 Q. PMNs, polymorphonuclear neutrophils, that is another
17 way of saying neutrophils?

18 A. Yes. That's an alternative designation for
19 neutrophils.

20 Q. The conclusion that you reached in this article was
21 that extravasated, which means a neutrophil that has left
22 the blood vessel and gone into the tissue, does not contain
23 iNOS message protein or enzymatic activity. Right?

24 A. That's correct.

25 MR. REED: No further questions, Your Honor.

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1 THE WITNESS: Your Honor, I would like to follow
2 that up.

3 THE COURT: Wait. We will have your attorney
4 take the floor now. No further questions on cross.

5 Correct?

6 MR. REED: That's right.

7 MS. WILLGOOS: I have a brief redirect.

8 REDIRECT EXAMINATION

9 BY MS. WILLGOOS:

10 Q. My first question is, can you please finish your
11 answer?

12 A. I am glad that the counselor brought this up. This
13 was an exciting study for us. This was performed on
14 patients undergoing peritoneal dialysis, which induces an
15 acute inflammatory response that allows for the
16 extravasation of neutrophils from the blood into the
17 peritoneal cavity. That's an acute inflammation. These
18 cells have a half-life of just a few hours. By the time we
19 get them, they are in various stages of apoptosis and dying.
20 It is a very different situation than a chronic inflammatory
21 the situation where neutrophils extravasate into the tissue,
22 the inflammatory mediators that are generating this
23 inflammatory response are known, well known in the
24 literature to maintain viability of the neutrophils and
25 allow them to up-regulate iNOS.

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1 Subsequent to our paper with the group at Yale,
2 it demonstrated that neutrophils collected from patients
3 with chronic glomular nephritis had up-regulated message
4 protein enzymatic activity. Patients with Crohn's and
5 ulcerative colitis, chronic inflammatory bowel disease,
6 neutrophils in that tissue are shown to have an up-regulated
7 iNOS.

8 Q. Mr. Reed asked you some requests about Dr. Webster's
9 testimony. I am not quite sure the two of us heard the same
10 testimony. I wanted to ask you some questions about what
11 you heard this morning. Did you hear Dr. Webster testify
12 that Oracea is the result of a dysregulated immune response?

13 A. Yes, I do.

14 Q. Agree or disagree with his conclusion?

15 A. Yes. I agree with his conclusion.

16 Q. Did you also hear Dr. Webster say that the cells of
17 rosacea include leukocytes, including neutrophils?

18 A. Yes, I did.

19 Q. Do you agree with that opinion?

20 A. I do.

21 Q. Did you --

22 MR. REED: Objection. This is leading
23 questioning.

24 THE COURT: Overruled. Go ahead.

25 BY MS. WILLGOOS:

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1 Q. Did you also hear Dr. Webster testify that the white
2 blood cells, those blood cells that we just discussed, form
3 the papules and pustules of Oracea?

4 A. Yes, I agree with that.

5 Q. Did you hear anything in Dr. Webster's testimony this
6 morning that contradicts your opinions regarding
7 up-regulation of iNOS in rosacea?

8 A. No.

9 Q. Now, Mr. Reed asked you questions regarding
10 quantitative data. Does your opinion that iNOS is
11 up-regulated and that tetracycline and 40 milligrams of
12 doxycycline decreased that up-regulation, does that rely or
13 require quantitative data?

14 A. No. I don't believe it does.

15 Q. Why not?

16 A. I believe it doesn't because the preponderance of
17 evidence tells us that when you have chronic inflammation of
18 rosacea or other tissues, there will be, there is no doubt
19 in the scientific community, there will be up-regulation of
20 iNOS, with pathogenic formation of NO and that the
21 literature also tells us that doxycycline will inhibit the
22 up-regulation of iNOS. And we know, it's already been
23 entered into evidence that 40 milligrams of doxycycline
24 treats the pustules and the papules associated with rosacea.

25 Q. How do you know that? Was that based on quantitative

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1 data?

2 A. Yes. That was based on a clinical study that was
3 reported in the Mylan product.

4 Q. Now, Dr. Grisham, if you could just turn to PTX-329.
5 It's in the witness binder you had this morning in your
6 direct. I would like to direct you to Page 647 of that
7 article?

8 A. Yes, ma'am.

9 Q. If I could just direct you under the second column
10 that talks about NO and inflammatory or immune mediated skin
11 diseases. If we could just blow out the rest of that
12 column, please?

13 Do you recall reviewing this article in forming
14 your opinions?

15 A. Yes, I do.

16 Q. What does this article tell you?

17 A. This article tells us that iNOS is in fact
18 up-regulated in chronic skin diseases. In fact, in a very
19 close cousin of rosacea, in psoriasis, there is in fact the
20 up-regulation in psoriatic inflammation, for example, which
21 is another chronic immune based dermal inflammation.

22 Q. And were these studies conducted in humans?

23 A. Yes, they were.

24 Q. How does that inform your opinion if at all regarding
25 the up-regulation of iNOS in rosacea?

1 A. I don't think there is any other conclusion but that
2 iNOS is up-regulated in chronic skin inflammation and in
3 rosacea specifically because the papules and pustules
4 associated with rosacea are simply collections of large
5 numbers of iNOS producing neutrophils. I think we
6 established that with Dr. Webster's testimony this morning.

7 MS. WILLGOOS: Thank you, Dr. Grisham. I have
8 no further questions.

9 THE COURT: Thank you. You can step down,
10 Doctor.

11 (Witness excused.)

12 THE COURT: You can call your next witness.

13 MS. WILLGOOS: At this time, Your Honor, we have
14 some deposition testimony. We have two clips of two
15 witnesses. We can play them together or separately, as Your
16 Honor wishes. They are only about ten minutes collectively.

17 THE COURT: Why don't you introduce them
18 separately. So do one at a time.

19 MS. WILLGOOS: Sure.

20 Your Honor, first we would like to call Stephen
21 Wayne Talton, Mylan's vice president in the regulatory area,
22 and we have, if Your Honor would like it, references that
23 will be discussed during the deposition clip.

24 THE COURT: That is fine, yes. If you pass up
25 two copies of each, that would be helpful. Are you going to

Talton - designations

1 be playing video or reading?

2 MS. WILLGOOS: Video.

3 Your Honor, if you would like, we also have the
4 clips of the transcript, if you would like to see that as
5 well.

6 THE COURT: Yes, please. Thank you.

7 Mr. Golden, I will ask you to go dim some of the
8 lights, please.

9 (Deposition played as follows:)

10 "Question: Could you please spell your name?

11 "Answer: Sure. It's Stephen Wayne Talton,
12 S-t-e-p-h-e-n, W-a-y-n-e, T-a-l-t-o-n.

13 "Question: I've handed you Plaintiffs'
14 Deposition Exhibit 4, a document bearing Bates range Mylan-D
15 000042 to MYL-D00044.

16 "What is this document?

17 "Answer: It appears to be a copy of the 356h
18 form that accompanied our original ANDA submission.

19 "Question: And, specifically, Mylan's original
20 ANDA submission for ANDA 90-855?

21 "Answer: That's correct.

22 "Question: Have you seen this document before?

23 "Answer: Yes.

24 "Question: When did you first see this
25 document?

Talton - designations

1 "Answer: When I signed it.

2 "Question: Since October 3, 2008, has Mylan
3 informed the FDA that any of the data or information in its
4 original ANDA submission 90-855 was, in fact, not true and
5 accurate?

6 "Answer: Not to my knowledge.

7 "Question: And, again, all communications with
8 the FDA regarding ANDA 90-855 went through you. Correct?

9 "Answer: That's correct.

10 "Question: Let me just say: Has Mylan made any
11 willfully false statements in ANDA 90-855?

12 "Answer: No, not to my knowledge.

13 "Mr. Diamond: We can mark this document
14 Plaintiffs' 14.

15 "Mr. Diamond: This is a document bearing
16 Bates number MYL-D118492 through 495.

17 "Question: This is another form 356h, right --

18 "Answer: Yes.

19 "Question: -- dated May 21, 2010?

20 "Answer: Correct.

21 "Question: And this, again, was submitted to
22 ANDA 90-855?

23 "Answer: Yes.

24 "Question: Okay. This document was signed by
25 you on May 21, 2010?

Talton - designations

1 "Answer: Yes.

2 "Question: And will Mylan -- Is Mylan allowed
3 to market pharmaceutical products for indications that are
4 not in the approved labeling for those pharmaceutical
5 products?

6 "Answer: We have to pursue approved labeling,
7 and that's what is with our product, and that's how it's to
8 be used in the marketplace.

9 "Question: To your knowledge, does Mylan have
10 any plans to market this generic product for any indication
11 other than "for the treatment of inflammatory lesions
12 (papules and pustules) of rosacea in adult patients"?

13 "Answer: Not to my knowledge.

14 "Question: Okay. To your knowledge, does Mylan
15 have any specific expectation that doctors will prescribe
16 this generic product for any indication other than "for the
17 treatment of inflammatory lesions (papules and pustules) of
18 rosacea in adult patients"?

19 "Answer: No, not to my knowledge.

20 "Question: Staying with plaintiffs' Exhibit 18,
21 Mr. Talton, can you turn to the page bearing Bates number
22 ending in 465. Do you see section 12.4, "Microbiology"?

23 "Answer: Yes.

24 "Question: Let me ask you a different question
25 then. To your knowledge, has Mylan provided any information

Talton - designations

1 to the FDA that its generic product would reduce the
2 number of microorganisms associated with any bacterial
3 disease?

4 "Answer: Not to my knowledge.

5 "Question: Okay. To your knowledge, has Mylan
6 provided any evidence to the FDA that its generic product
7 would eliminate microorganisms associated with any bacterial
8 disease?

9 "Answer: Not to my knowledge. We do
10 bioequivalence studies to support our ANDA.

11 "Question: So it would be your expectation that
12 Mylan wouldn't have any such information in its possession.
13 Right?

14 "Answer: I told you what type of studies we do
15 to support an ANDA registration. There are PK studies.

16 "Question: So, to your knowledge, Mylan doesn't
17 have any evidence that its generic product would eliminate
18 microorganisms associated with any bacterial disease.

19 Right?

20 "Answer: Not to my knowledge.

21 "Question: Is Mylan aware of any in vivo
22 microbiology studies of Mylan's generic product or a product
23 with similar drug exposure that would demonstrate a
24 detectable long-term effect on bacterial flora of the oral
25 cavity, skin, intestinal tract, or vagina?

Talton - designations

1 "Answer: I'm not aware of any such studies.

2 "Question: Is Mylan aware of any such studies?

3 "Answer: No, not to my knowledge.

4 "Question: Is Mylan aware of any in vivo
5 microbiology studies of Mylan's generic product or a product
6 with a similar drug exposure that demonstrates detectable
7 long-term effects on the bacterial flora at any site in
8 the human body other than the sites I mentioned earlier,
9 which were oral cavity, skin, intestinal tract, and vagina?

10 "Answer: I'm not aware of any such studies.

11 The information that's in our label is the same as the
12 reference product. That's why it's in our label.

13 "Question: Is Mylan aware of any studies
14 demonstrating that Mylan's generic product would result in a
15 reduction of the bacterial flora of the skin during a
16 six-month treatment?

17 "Answer: I'm not aware of any such studies.

18 "Question: And is Mylan aware of any such
19 studies?

20 "Answer: Not to my knowledge.

21 "Question: "Vice President, Regulatory
22 Affairs," that's your correct position. Right?

23 "Answer: Yes.

24 (Designation ends.)

25 MS. WILGOOS: Your Honor, Tim Galderma would

Wargo - designations

1 like to move into evidence DTX-2261, DTX-2271, and DTX-2275
2 based on Mr. Talton's testimony.

3 THE COURT: Any objection?

4 MR. STEUER: No objection.

5 THE COURT: They are admitted.

6 (DTX-2261, DTX-2271, and DTX-2275 received into
7 evidence.)

8 MS. WILGOOS: Thank you, your Honor.

9 Next is deposition clip of David Wargo, another
10 Mylan's corporate representatives in a Rule 30(b) (6)
11 capacity of his deposition.

12 THE COURT: Do you want to pass up documents?

13 MS. WILGOOS: There are no documents.

14 (Deposition of David J. Wargo placed into the
15 record.

16 "Question: Would you please state your name and
17 address?

18 for the record?

19 "Answer: David J. Wargo, 315 Parkside Avenue,
20 Pittsburgh, Pennsylvania, 15228.

21 "Question: Do you understand that Mylan
22 currently markets 50, 100, and 150 milligram antibiotic
23 doses of doxycycline?

24 "Answer: Yes.

25 "Question: Would a 40 milligram instant-release

Wargo - designations

1 version of Mylan's generic product be bioequivalent to
2 Oracea?

3 "Answer: I don't know. You'd have to conduct
4 that study.

5 "Question: Is it your understanding that the
6 50, 75, 100, and 150 milligram products are immediate
7 release? I think you said that.

8 "Answer: Yes.

9 "Question: Does Mylan have any evidence that
10 its generic Oracea product would inhibit the growth of
11 Microorganisms?

12 "Answer: No, I don't believe we've studied it
13 in that capacity.

14 "Question: So Mylan hasn't studied whether its
15 generic product will inhibit the growth of microorganisms.
16 Correct?

17 "Answer: That's correct.

18 "Question: Mylan hasn't studied whether Oracea
19 will inhibit the growth of microorganisms. Correct?

20 "Answer: Correct.

21 "Question: Has Mylan performed any steady state
22 pharmacokinetic studies on its generic product?

23 "Answer: We have not.

24 "Question: Did Mylan try at all to design
25 around the formulation of branded Oracea?

1 "Answer: Not that I recall.

2 (Deposition designations end.)

3 THE COURT: Is that it for the depositions?

4 MR. FLATTMANN: Yes, your Honor. That's the end
5 of our proffered deposition clips.

6 THE COURT: Let's bring the lights back on.

7 And what is next?

8 MR. FLATTMANN: Your Honor, that represents the
9 end of Galderma's case-in-chief.

10 THE COURT: Okay. Fine. The defense can call
11 their witness.

12 MR. REED: Your Honor, at this time we would
13 like to make a motion.

14 THE COURT: A motion okay? Come to the podium.

15 MR. REED: Mylan moves pursuant to Federal Rule
16 of Civil Procedure 52(c) for judgment on partial findings
17 with respect to three of the five patents: both of the
18 Amin patents and the Chang patent for judgment of
19 noninfringement.

20 With respect to the Amin patents, plaintiffs
21 have failed to adduce any evidence that a 40-milligram daily
22 dose of doxycycline would infringe any of the asserted
23 claims.

24 With respect to the Chang patent, the only data
25 that plaintiffs have adduced with respect to infringement of

1 claims 4 and 18 overwhelmingly shows that the 40-milligram
2 daily dose of doxycycline contained in Mylan's product would
3 not provide blood plasma, steady state blood plasma levels
4 of between .3 micrograms per milliliter and .8 micrograms
5 per milliliter.

6 THE COURT: Thank you. Any response?

7 MR. FLATTMANN: Yes, your Honor. Galderma
8 opposes Mylan's motion. We have presented through the
9 testimony of Dr. Grisham and beyond a preponderance of the
10 evidence proof that the Amin patent claims will be
11 infringed. Those proofs have not been rebutted in any way
12 by Mylan.

13 With regard to the Chang patents, by Mylan's own
14 admission it infringes the two dependent claims of the Chang
15 patent.

16 As we saw on the slide that we presented to the
17 Court earlier today, slide PDX-22, Mylan has admitted both
18 of the preliminary injunction hearing and in statement of
19 contested facts at paragraph 39 that the serum concentration
20 is achieved at steady state, with its patients, will fall
21 within the range of .3 micrograms per mil to .8 micrograms
22 per mil. In addition, the evidence that was presented by
23 Dr. Rudnic from the Mylan label confirms those admissions.

24 So with regard to both motions, Galderma
25 opposes.

1 THE COURT: Okay. Thank you.

2 MR. FLATTMANN: Thank you.

3 THE COURT: The Court is going to reserve
4 judgment on the Rule 52(c) motion. We'll hear the rest of
5 the evidence and we'll get the briefing following trial.

6 And with that, we'll turn to the defense to call
7 your witness.

8 MR. FLATTMANN: Thank you, your Honor.

9 MR. REED: Thank you, your Honor. As our first
10 witness we call Dr. Lawrence Feldman via deposition.

11 THE COURT: Okay. We'll go ahead and dim the
12 lights again.

13 MR. REED: Your Honor with respect to
14 Dr. Feldman's testimony, we will move for the admission of
15 Exhibit DTX-1559, which is the patient record which has
16 already been discussed by other witnesses as well.

17 THE COURT: Any objection?

18 MR. FLATTMANN: No objection, your Honor.

19 THE COURT: Okay. It's admitted.

20 (DTX-1559 received into evidence.)

21 THE COURT: Is Dr. Feldman's testimony going to
22 take us beyond 6:00 o'clock?

23 MR. REED: I think it might come in almost at
24 6:00 o'clock. I don't know.

25 MR. STEUER: It's an hour and seven minutes,

Feldman - designations

1 your Honor.

2 THE COURT: An hour and seven minutes.

3 We'll go to 6:00 and then we'll watch the last
4 bit of it tomorrow morning.

5 (Deposition designations of Dr. Lawrence Feldman
6 placed into the record.)

7 "Question: Would state your full name, please?

8 "Answer: Lawrence Richard Feldman.

9 "Question: And your residence address?

10 "Answer: 1 Garrison Forest Road, Owens Mill,
11 Maryland 21117.

12 "Question: By whom are you employed,
13 Dr. Feldman?

14 "Answer: By myself.

15 "Question: And is there a legal entity under
16 which you practice?

17 "Answer: Yes. It's Lawrence R. Feldman MD, PC.

18 "Question: And can I refer to that entity as
19 Feldman PC just for short?

20 "Answer: Yes.

21 "Question: For how long have you been
22 practicing as Feldman PC?

23 "Answer: 25 years.

24 "Question: So since roughly 1985?

25 "Answer: Yes.

Feldman - designations

1 "Question: And do you have an area of specialty
2 in the practice?

3 "Answer: General dermatology.

4 "Question: For how long have you been
5 practicing as a dermatologist?

6 "Answer: 25 years.

7 "Question: Since forming Feldman PC in 1985,
8 have any other dermatologists practiced with you as part of
9 Feldman PC?

10 "Answer: Yes.

11 "Question: How many different dermatologists
12 have practiced with you?

13 "Answer: Three.

14 "Question: And during what periods of time?

15 "Answer: 2004 to 2005 for one year, 2005 to
16 2006 for one year, and then 2008 and on.

17 "Question: So no one practiced with you prior
18 to 2004?

19 "Answer: No.

20 "Question: Okay. Where did you go to college,
21 sir?

22 "Answer: The University of Maryland at College
23 Park.

24 "Question: And what was your major?

25 "Answer: Psychology.

Feldman - designations

1 "Question: When did you graduate?

2 "Answer: 1977.

3 "Question: And when did you enroll in medical
4 school?

5 "Answer: 1977.

6 "Question: And where was that, sir?

7 "Answer: University of Maryland at Baltimore.

8 "Question: And when did you graduate from
9 medical school?

10 "Answer: 1981.

11 "Question: After graduating from medical
12 school, did you obtain any further medical training?

13 "Answer: Yes.

14 "Question: What type?

15 "Answer: I did a one year internship in
16 internal medicine from 1981 to 1982 at the Mercy Medical
17 Center in Baltimore, and then from 1982 to 1985 I did a
18 three-year residency in dermatology at the University of
19 Pittsburgh in Pittsburgh, Pennsylvania.

20 "Question: Have you had any other formal
21 training in medicine apart from what you described?

22 "Answer: No.

23 "Question: Are you familiar with the concept of
24 board certification in particular areas of medicine?

25 "Answer: Yes.

Feldman - designations

1 "Question: Do you have any board certifications
2 in dermatology?

3 "Answer: Yes.

4 "Question: What certifications do you have?

5 "Answer: I'm board certified by the State of
6 Maryland as a certified specialist in dermatology.

7 "Question: Any other certifications?

8 "Answer: No.

9 "Question: And when did you receive your
10 certification?

11 "Answer: In 1987.

12 "Question: Is that a certification in
13 dermatology generally or some specialty of dermatology?

14 "Answer: General dermatology.

15 "Question: Have you ever testified before in a
16 deposition or at trial?

17 "Answer: Yes.

18 "Question: Which one? Deposition?

19 "Answer: Both.

20 "Question: Both. On how many occasions?

21 "Answer: Approximately ten times.

22 "Question: In what types of cases have you
23 testified?

24 "Answer: I have been an expert witness in
25 several cases regarding skin cancer. I just testified in a

Feldman - designations

1 case in Delaware in a case involving a young boy that was
2 given a cream to use in his groin area and developed stretch
3 marks and sores in his groin. That is the last one that I
4 testified in.

5 "Question: Were these malpractice cases or
6 other types of cases?

7 "Answer: Malpractice cases.

8 "Question: And in the cases that you have
9 testified, have you given testimony as a fact witness or as
10 an expert witness?

11 "Answer: Expert witness.

12 "Question: And in what field was your
13 expertise?

14 "Answer: Dermatology.

15 "Question: Are you familiar with the skin
16 disorder or disease -- I'm not sure which one it is -- but
17 one of those known as rosacea?

18 "Answer: Yes.

19 "Question: And in your experience as a
20 dermatologist, is rosacea sometimes also referred to as acne
21 rosacea?

22 "Answer: Yes.

23 "Question: And over the course of your career
24 as a dermatologist, have you treated patients who are
25 afflicted with rosacea?

Feldman - designations

1 "Answer: Yes.

2 "Question: What is rosacea in layman's terms
3 according to your understanding today?

4 "Answer: Rosacea is a condition of the skin
5 where your -- specifically, the middle third of your face
6 gets very red, flushed. You develop pimples, bumps on the
7 skin. You can also develop broken blood vessels of the skin
8 and at the ultimate stage you can develop something called
9 rhinophyma, which is also known as W.C. Fields nose. You
10 get a big red bulbous nose.

11 "Question: According to your understanding
12 today, can you tell us whether or not rosacea is a bacterial
13 disorder or bacterial disease?

14 "Answer: It is not thought to be a bacterial
15 disorder.

16 "Question: Did you have the same understanding
17 or a different understanding about that subject in the '99
18 to 2000 time frame?

19 "Answer: Same. Same understanding.

20 "Mr. Shulman: Let me have mark or have marked,
21 please, as Exhibit 1 a copy of a declaration of Dr. Feldman.

22 "Can you explain to us how you were involved in
23 drafting this document?

24 "Answer: I was contacted regarding this case.
25 I was then told about the records that were to be located

Feldman - designations

1 after I located the record and discussed it with
2 Mr. Delafield. He wrote up this declaration and sent it to
3 me by e-mail. I read it over and saw that it was what I,
4 you know, was the truth and then I signed it.

5 "Question: Did you make any changes to the
6 declaration before signing it?

7 "Answer: I did. I believe that there was a
8 typographical error that I noticed and I had that changed.

9 "Question: Any other changes that you can now
10 recall making to the document before signing it?

11 "Answer: I don't remember any others.

12 "Question: Before signing this declaration, did
13 you read it?

14 "Answer: Yes.

15 "Question: And before signing the declaration,
16 did you satisfy yourself that every statement you made in
17 this document was true and correct to the best of your
18 knowledge?

19 "Answer: Yes.

20 "Question: Have you ever heard of a
21 prescription drug by the name of Periostat?

22 "Answer: Yes.

23 "Question: When did you first become aware of
24 Periostat?

25 "Answer: I became first aware of Periostat in

Feldman - designations

1 the late 1990s.

2 "Question: And how did you become aware of
3 Periostat in the late 1990s?

4 "Answer: At that time, I had attended a
5 dermatology convention/meeting and one of the speakers
6 discussed the fact that Periostat could be used for
7 conditions such as acne rosacea.

8 "Question: And where was this conference?

9 "Answer: It was in Las Vegas, Nevada.

10 "Question: And you said in the 1990s. Can you
11 by any more specific about the year?

12 "Answer: It was around either 1998 or 1999.

13 "Question: And how do you pinpoint the time
14 frame?

15 "Answer: Well, because, number one, I know that
16 before I used Periostat in my own practice that I had heard
17 about it at a meeting, and, number two, in 2000, I had a
18 physician's assistant join me. And I know that once she
19 joined me, I didn't go on any of these meetings for awhile
20 because I wanted to be around while she was practicing, so I
21 know it was before 2000.

22 "Question: And do you know if it was in 1997 or
23 '98 or 99?

24 "Answer: I don't remember exactly.

25 "Question: Do you know what time of the year

Talton - designations

1 the conference was held?

2 "Answer: I do know that, because my wife went
3 with me and it was -- we went because it was her birthday,
4 which is October 21st, and the meeting was in October.

5 "Question: Okay. Who was the sponsor of the
6 conference, if you can recall?

7 "Answer: Westwood Dermatologists. Called the
8 Westwood Fall Dermatology Meeting. Westwood is a
9 pharmaceutical company.

10 "Question: I see. Do you recall who the
11 speaker was that spoke about Periostat to which you
12 referred?

13 "Answer: I do not.

14 "Question: Do you recall how many people were
15 in attendance at the speaking engagement where this person
16 spoke about Periostat?

17 "Answer: I would say approximately a hundred.

18 "Question: And you have told us generally what
19 he or she -- was it a he or a she?

20 "Answer: It was a he.

21 "Question: Do you recall who that speaker was?

22 "Answer: I do not.

23 "Question: Do you recall from where that
24 speaker came?

25 "Answer: I do not.

Talton - designations

1 "Question: Can you tell us as best you can
2 recall exactly what the speaker said about Periostat on the
3 occasion of this conference?

4 "Answer: The speaker was generally talking
5 about off-label uses of medication. They are sometimes
6 called dermatology pearls, so you go to these conferences so
7 you can hear newer ideas, things that are not in the
8 mainstream but newer ideas. And he was talking about newer
9 things to treat certain conditions and he mentioned
10 Periostat as being a treatment for rosacea.

11 "Question: Did he explain or can you tell us
12 whether or not he explained why Periostat might be useful to
13 treat rosacea?

14 "Answer: He said that was because it had an
15 anti-inflammatory effect and that one of the key
16 pathophysiology components of rosacea was inflammation of
17 the skin.

18 "Question: Can you tell us whether or not he
19 explained what Periostat was approved for by the FDA?

20 "Answer: Yeah. He said it was approved for
21 gingivitis.

22 "Question: Did the -- can you tell us whether
23 or not the speaker said that he had used Periostat to treat
24 rosacea?

25 "Answer: I don't remember if he had personally

Talton - designations

1 used it but he said that he had experience with it so I
2 don't know if it was him or somebody in his department had
3 used it. But he said he did have experience using it.

4 "Question: But you don't recall for what
5 purpose?

6 "Answer: No. For rosacea. But what I don't
7 know is whether it was exactly the speaker that had said
8 that he had used it or someone in his department. He just
9 said that he had experience with using Periostat for
10 rosacea.

11 "Question: Okay. As of mid-February in the
12 year 2000 did you know whether or not Periostat contained
13 the compound known as doxycycline?

14 "Answer: Yes.

15 "Question: And what did you know?

16 "Answer: I knew that it contained 20 milligrams
17 of doxycycline.

18 "Question: Okay. As of mid-February in the
19 year 2000 did you know whether or not Periostat contained
20 any active pharmaceutical ingredient other than doxycycline?

21 "Answer: No. No. I didn't know it contained
22 anything other than doxycycline.

23 "Question: As of mid-February in the year 2000
24 did you know whether or not each tablet of Periostat
25 contained 20 milligrams of doxycycline?

Talton - designations

1 "Answer: Yes.

2 "Question: Now, have you personally ever been
3 inflicted with the condition known as adult gingivitis?

4 "Answer: Yes.

5 "Question: And did you ever seek medical
6 treatment for that gingivitis condition?

7 "Answer: Yes.

8 "Question: And when did you seek medical
9 treatment for that condition?

10 "Answer: In 1999.

11 "Question: And were you ever prescribed
12 medication for your gingivitis?

13 "Answer: Yes.

14 "Question: And what medication were you
15 prescribed for your gingivitis in 1999?

16 "Answer: Periostat.

17 "Question: Did you take the prescribed
18 medication?

19 "Answer: Yes.

20 "Question: Was your Periostat prescription
21 for -- can you tell us what the prescription of Periostat
22 was for your gingivitis?

23 "Answer: It was Periostat 20 milligrams, take
24 one tablet twice daily.

25 "Question: And did you take this prescription

Talton - designations

1 prior to mid-February of the year 2000?

2 "Answer: Yes.

3 "Question: For about how long prior to
4 mid-February of 2000 did you take the Periostat
5 prescription?

6 "Answer: Five to six weeks.

7 "Question: Have you personally ever been
8 inflicted with rosacea?

9 "Answer: Yes.

10 "Question: Can you tell us whether or not you
11 had rosacea during the time you were taking Periostat for
12 your gingivitis condition?

13 "Answer: I did.

14 "Question: In the time period prior to
15 mid-February of 2000 when you were taking your Periostat
16 prescription, did the Periostat help your gingivitis
17 condition?

18 "Answer: Yes.

19 "Question: In that same period prior to
20 mid-February of 2000 when you were taking the Periostat for
21 your gingivitis condition, can you tell us whether or not
22 you noticed any change in your rosacea?

23 "Answer: I did notice a change in my rosacea.

24 "Question: What change did you notice?

25 "Answer: It seemed to get better.

Talton - designations

1 "Question: At the time that you noticed this
2 change, to what, if anything, did you attribute the change
3 in your rosacea condition?

4 "Answer: I attributed it to the Periostat.

5 "Question: And why did you attribute it to the
6 Periostat?

7 "Answer: Because it was the only thing
8 different that I had done. It was the only change that had
9 occurred that was taking the Periostat. Nothing else
10 changed in my condition.

11 "Question: Can you tell us whether or not your
12 personal experience with taking Periostat in late '99 and
13 early 2000 and your rosacea condition, did that have any
14 impact on your treatment of patients who had rosacea?

15 "Answer: It did. Because I had an improvement
16 with Periostat I thought that this might be something that I
17 could use to help other patients with rosacea.

18 "Question: And when did you reach that
19 conclusion, for lack of a better term?

20 "Answer: In January of 2000.

21 "Question: In the first sentence of Paragraph 2
22 you stated that 'Attached to this declaration is Exhibit A,
23 which a Feldman, P.C. patient record dated February 19,
24 2000.'

25 "Do you see that?

Talton - designations

1 "Answer: Yes.

2 "Question: Is the final page of this
3 declaration this copy of this patient report that was made,
4 this paragraph?

5 "Answer: Yes.

6 "Question: In whose handwriting is this patient
7 report written?

8 "Answer: That's mine.

9 "Question: Is that your signature at the bottom
10 of the patient record?

11 "Answer: Yes.

12 "Question: Did you write down the information
13 that appears on this patient record.

14 "Answer: Yes.

15 "Question: On what date did you do so.

16 "Answer: On February the 19th of 2000.

17 "Question: Did you have -- can you tell us
18 whether or not you had any standard practice in February of
19 2000 about when you prepared a patient record relative to
20 the time you saw the patient that is the subject of the
21 record?

22 "Answer: My normal routine was to write out the
23 patient record while I was seeing the patient so that it
24 would be done before the visit was done.

25 "Question: And that was your standard practice

Talton - designations

1 at the time?

2 "Answer: Yes.

3 "Question: Can you tell us whether or not you
4 have any reason to believe that you did not follow your
5 standard practice with respect to the patient record that is
6 Exhibit A to your declaration?

7 "Answer: No.

8 "Question: Now, is the original of the patent
9 record, Exhibit A, located in a facility of Feldman, P.C.?

10 "Answer: Yes.

11 "Question: And can you tell us what that
12 facility is?

13 "Answer: Yes. I maintain a storage unit at
14 Easy Storage and we have there boxes of charts for patients
15 that have been retired and that are kept in storage.

16 "Question: The patients are retired or the
17 charts are retired?

18 "Answer: The charts are retired.

19 "Question: Can you explain to us what you mean
20 by a retired chart?

21 "Answer: Yes. So our normal routine is that if
22 someone is seen in the office and then does not come back
23 for a return visit for one year, we go ahead then and take
24 that chart apart. We take the records out of the manila
25 folder and we put it into a storage box and store it at the

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1 storage unit.

2 "Question: When you say you take the chart
3 apart, what does a chart consist of?

4 "Answer: Usually it has a demographic page so
5 it has a page of their name and address and insurance. It
6 has a medical history page that talks about what medications
7 they are on, what allergies they have. It has a page that
8 says why they are coming -- why they started to come to see
9 us and then it has notes from the dates of service.

10 "Question: And all of this, before retirement,
11 is maintained in some sort of manual folder?

12 "Answer: Yeah. And then that's kept in our
13 office in the active chart file in Westminster.

14 "Question: And when you retire the chart, if I
15 am understanding you correctly, you take these documents
16 located in the manila folder and place them in storage?

17 "Answer: Yes, because we don't have -- we
18 wouldn't have enough room. If we just started keeping all
19 the charts, we would run out of room.

20 "Question: But you don't actually place the
21 manila folder into storage?

22 "Answer: No.

23 "Question: Now, has the original of the patient
24 record, Exhibit A to your declaration, been in the custody
25 and control of Feldman, P.C. since you wrote it in February

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1 of 2000?

2 "Answer: Yes.

3 "Question: Now, up at the top of Exhibit A to
4 your declaration the name of the patient and the patient's
5 date of birth have been scratched out. Do you see that?

6 "Answer: Yes.

7 "Question: Does the original of Exhibit A have
8 the name of the patient and the date of birth scratched out?

9 "Answer: Yes.

10 "Question: The original does?

11 "Answer: Yes.

12 "Question: Let me explain what I mean by the
13 original. Not the one that you make a copy of in order to
14 produce to us, but your original patient record that is
15 stored.

16 "Answer: Oh, oh. I'm sorry. No.

17 "Question: Let me just get the question clear
18 on the record so there is no confusion. When I refer to the
19 original of Exhibit A I mean the patient record that you
20 actually created on February 19th.

21 "Answer: Right. No.

22 "Question: With that definition of original,
23 does the original of Exhibit A have the name of the patient
24 and the date of birth scratched out?

25 "Answer: No.

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1 "Question: Who scratched out the name of the
2 patient and the date of birth on Exhibit A to your
3 deposition?

4 "Answer: I did.

5 "Question: Just wait until I finish. It makes
6 it easier for her.

7 "Answer: Okay.

8 "Question: Why did you scratch out the name of
9 the patient and the birth date on Exhibit A?

10 "Answer: Because when Mr. Delafield asked me to
11 look through records and I found this record, he wanted me
12 to send it to him and I didn't -- I think you are not
13 allowed to transmit something that would identify who the
14 patient was. So I went ahead and scratched out so there
15 wouldn't be any violation of her privacy.

16 "Question: And in Paragraph 5 of your
17 declaration, you refer to obligations you have under the
18 Health Insurance Portability and Accountability Act?

19 "Answer: Yes.

20 "Question: What is that?

21 "Answer: That's called HIPAA, which is that
22 when a patient sees me they have a right to privacy of
23 anything regarding their medical information.

24 "Question: And so did you scratch out the name
25 of the patient and the date of birth of the patient pursuant

Talton - designations

1 to this HIPAA?

2 "Answer: Yes.

3 "Question: Okay. Apart from the scratched out
4 patient name and date of birth in Exhibit A is Exhibit A, is
5 there anything different than the original patient record
6 that you maintain in your office?

7 "Answer: It's exactly the same.

8 "Question: Now, when did you make the copy of
9 the original patient record that we see as Exhibit A?

10 "Answer: Right before I sent it to Mr.
11 Delafield.

12 "Question: That was in which month?

13 "Answer: I think it was in June -- May or June
14 of this year.

15 "Question: Do you have any reason to believe
16 that the original patient record that you maintained in
17 storage was altered in any way since the time that you wrote
18 that record in February of 2000 up through the date that you
19 made the copy in June of this year?

20 "Answer: No, it wouldn't be altered.

21 "Question: Apart from the scratched out patient
22 name and the date of birth is Exhibit A identical to the
23 original patient record in your office?

24 "Answer: Yes.

25 "Question: Now, let me ask you a few questions

Talton - designations

1 about the record itself.

2 "The first entry appears to say in the printed
3 portion, 'CC: And then handwritten, red face/pimples'?

4 "Answer: Yes.

5 "Question: Have I read that accurately?

6 "Answer: That's correct.

7 "Question: What does that entry mean?

8 "Answer: CC is the chief complaint. That's the
9 reason she came to see me for that visit.

10 "Question: And so what is the meaning of the
11 handwritten entry next to chief complaint?

12 "Answer: That was what she was complaining of.
13 She said that her face -- she had had a red face and that
14 there were pimples on her face.

15 "Question: Okay. Underneath that there is
16 another handwritten entry or printed entry that appears to
17 say HPI. Is that correct?

18 "Answer: Uh-huh.

19 "Question: What does that stand for?

20 "Answer: History of present illness.

21 "Question: And that is sort of the topic
22 heading for the next several entries?

23 "Answer: Uh-huh.

24 "Question: All right. And the next entry says
25 location in printed form and then it says in handwritten,

Talton - designations

1 cheeks, nose, chin. Have I read that correctly?

2 "Answer: Yes.

3 "Question: What does that mean?

4 "Answer: That's where she had the -- that's the
5 area where the rash was on her face.

6 "Question: The next printed entry says quality
7 and then there is something written after that that I can't
8 make out.

9 "Answer: Do you want me to read it?

10 "Question: If you could, please.

11 "Answer: It says, complaint. O stands for
12 complaint of the -- that the sun stings. That when she is
13 out in the sun that she gets stinging on her face.

14 "Question: That is something she told you?

15 "Answer: Yes.

16 "Question: And then the next entry is severity
17 and you wrote moderate?

18 "Answer: Yes.

19 "Question: What does that mean?

20 "Answer: That was how she described how severe
21 the condition was.

22 "Question: And then the next entry says
23 duration and there is some pencil mark, and then a 6 and
24 then it says weeks.

25 "Can you tell us what the entry is there?

Talton - designations

1 "Answer: Yes. Greater than six weeks.

2 "Question: And what does that mean?

3 "Answer: She has had this problem for more than
4 six weeks.

5 "Question: The next entry is timing, and I
6 can't make out what you said thereafter.

7 "Answer: Worse after heat.

8 "Question: What does that signify?

9 "Answer: It meant that when she got hot that
10 her skin got worse, her condition got worse.

11 "Question: And then there is an entry that says
12 modifying and factors next to which you wrote face surface
13 flushed, I think?

14 "Answer: Yes.

15 "Question: And what does that mean?

16 "Answer: It means that she complained that her
17 face was constantly red and flushed.

18 "Question: And then it says context and I can't
19 read what is after that.

20 "Answer: Very bright red.

21 "Question: What does that mean?

22 "Answer: It means that she was upset because
23 her skin was staying very red.

24 "Question: And then there is something that
25 says ASSOC, I believe SX and SX?

Talton - designations

1 "Answer: It stands for associated signs and
2 symptoms.

3 "Question: And you wrote new pimples?

4 "Answer: New pimples, exactly.

5 "Question: And what is the meaning of that
6 entry?

7 "Answer: That she was developing new pimples on
8 her face.

9 "Question: The next entry says P.F.S. HX.

10 "What does that mean?

11 "Answer: That means past family and social
12 history.

13 "Question: And you wrote what next to that?

14 "Answer: Positive rosacea. She had a positive
15 family history for rosacea.

16 "Question: And the next entry is ROS. What
17 does that stand for?

18 "Answer: Review of systems.

19 "Question: And what did you write next to that?

20 "Answer: Feels well without any other --
21 without other skin complaints.

22 "Question: That is what she told you?

23 "Answer: Yes.

24 "Question: The next entry is PE.

25 "What does that stand for?

Talton - designations

1 "Answer: Physical exam.

2 "Question: And what did you write next to that?

3 "Answer: Bright red face with broken vessels

4 and pustules.

5 "Question: And what does pustules mean?

6 "Answer: Pimples. The medical term for

7 pimples.

8 "Question: Underneath that it says MDM. What
9 does that stand for?

10 "Answer: It's basically the diagnostic -- what
11 your diagnosis is.

12 "Question: And can you read the first line of
13 your diagnosis?

14 "Answer: It says diagnosis rosacea.

15 "Question: Can you read the next line, please?

16 "Answer: Next line is: The plan discussed with
17 patient regarding treatment for rosacea. Will use Periostat
18 20 milligrams BID due to its anti-inflammatory effect with
19 decreased risk of side effects.

20 "Question: And then it says RTC-3 months?

21 "Answer: Right. It says return to clinic in
22 three months. And then there is a copy of the -- of what I
23 had written as her prescription.

24 "Question: Can you read the prescription on the
25 right, please?

Talton - designations

1 "Answer: Periostat, 20 milligrams, one PO BID,
2 No. 180, refill times one. And then it has my signature.

3 "Question: Let me just ask you a few questions
4 about this entry under MDM.

5 "Answer: Uh-huh.

6 "Question: When you wrote diagnosis rosacea,
7 was that your diagnosis of her condition?

8 "Answer: Yes.

9 "Question: I'm sorry. I have forgotten what
10 you said this next line reads. Could you read it to me
11 again?

12 "Answer: Sure. Plan discussed. D/W means I
13 discussed with the patient regarding the treatment for
14 rosacea and I put that I will use Periostat 20 milligrams
15 BID due to its anti-inflammatory effect with a decreased
16 risk of side effects.

17 "Question: And Periostat is the same as
18 Periostat that we spoke about earlier today?

19 "Answer: Yes.

20 "Question: What does 20 milligrams bid mean?

21 "Answer: That is the dosage so that they are 20
22 milligram tablets and she was to take them twice daily.

23 "Question: BID means twice daily?

24 "Answer: Yes.

25 "Question: Is that Latin or something?

Talton - designations

1 "Answer: Yes.

2 "Question: What did you mean by due to its
3 anti-inflammatory effect with diminished risk of side
4 effects?

5 "Answer: Well, as I said, I had been to this
6 conference and they had talked about the fact that Periostat
7 had been used for rosacea for its anti-inflammatory effects,
8 so I was noting in the chart that this was my rationale
9 because this was an off-label use of a medicine and so
10 rather than just write out the prescription I wanted to mark
11 down my sort of medical theory or justification for why I
12 was doing that.

13 "Question: Okay. And what did you mean by with
14 reduced or diminished risk of side effects?

15 "Answer: Well, because it's a lower dose of
16 doxycycline, I thought that she would have less problems
17 with photosensitivity or GI upset, other things that are
18 common to people who take higher doses of doxycycline."

19 "Question: What caused you to write down
20 diminished risk of side effects when you were prescribing
21 this Periostat?

22 "Answer: Because, again, I wanted to make sure
23 that there was -- it was clear that there was a reason if
24 somebody ever questioned why I did this, that there was a
25 reason why I had given Periostat for rosacea since it was

Talton - designations

1 off-label.

2 "Question: Okay. And did you -- was there a
3 source of knowledge that caused you to write down that there
4 was a diminished risk of side effects?

5 "Answer: Well, I knew that -- I knew from my
6 own medical judgment and knowledge that there was a reduced
7 risk of side effects due to the reduced dosage and also my
8 personal usage of it, I knew that it was reduced.

9 "Question: All right. Now, you said RF times
10 one?

11 "Answer: Yes.

12 "Question: Over on the right there?

13 "Answer: Yes.

14 "Question: Does that mean one refill?

15 "Answer: Yes. She was given one refill.

16 "Question: And number 180, that entry means
17 what, sir?

18 "Answer: She was given a prescription for 180
19 tablets.

20 "Question: Taken twice a day?

21 "Answer: Taken twice it a day. So it was a
22 three-month supply with an extra refill.

23 "Question: So for a total of six months?

24 "Answer: Yes.

25 "Question: Up at the top right underneath the

Talton - designations

1 pictures of hands and bodies and faces, there is something
2 that you wrote there which I can't make out. Could you tell
3 us what it is?

4 "Answer: Yeah. It says, Saturday visit, the
5 patient was a teacher.

6 "Question: So she visited you on a Saturday?

7 "Answer: Yes.

8 "Question: Does this patient record, Exhibit A
9 to your declaration, accurately describe the method that you
10 used on or about February 19, 2000 to treat the rosacea
11 condition of the patient who is the subject of this record?

12 "Answer: Yes.

13 "Question: Dr. Feldman, with respect to Exhibit
14 A to your declaration, can you please describe to us the
15 communications that you had which led to your locating this
16 record and what you did to locate the record?

17 "Answer: Yes. Mr. Delafield contacted me and
18 said that they were interested in this case about rosacea
19 and Periostat and was wondering if I had any records
20 regarding patients that may have taken Periostat in this
21 time frame of 2000. And I told him that I would go ahead
22 and search through the storage unit, storage boxes, and try
23 to find if I had written for any patients Periostat, and so
24 I did that. And then I found this record and contacted him,
25 and he asked me to make a copy of it and send it to him, and

Talton - designations

1 then he wrote up this declaration and I signed it.

2 "Question: And were you compensated for the
3 time that you put in for the -- for the time that you spent
4 doing what you just described?

5 "Answer: Yes.

6 "Question: And how much were you compensated on
7 an hourly basis?

8 "Answer: \$500 per hour.

9 "Question: Are we paying you for your time here
10 today?

11 "Answer: No.

12 "Question: And you understand that we are not
13 allowed to do so?

14 "Answer: Yes.

15 "Question: Let me show you February 19th or the
16 calender for February of 2000.

17 "Can you confirm what day of the week
18 February 19th was?

19 "Answer: It's a Saturday.

20 "Question: And that's consistent with your
21 record?

22 "Answer: Yes.

23 "Question: Can you tell us whether or not you
24 prescribed Periostat to the patient in Exhibit A because of
25 the antibiotic properties of doxycycline?

Talton - designations

1 "Answer: Can I?

2 "Question: Okay. You can answer.

3 "Answer: I prescribed it for its

4 antiinflammatory effect.

5 "Question: And how did you know that Periostat
6 had antiinflammatory properties when you prescribed it to
7 the patient in Exhibit A?

8 "Answer: I had learned about it at the
9 dermatology meeting that I had been to. It had been in
10 several what they call throwaway publications. There had
11 been articles about Periostat, and also I had used it
12 personally and was told by the periodontist that it had an
13 antiinflammatory effect.

14 "Question: Can you tell us whether or not you
15 regarded the antiinflammatory properties of Periostat
16 important to treating the rosacea of the patient in Exhibit
17 A?

18 "Answer: I did.

19 "Question: And why did you regard it as
20 important?

21 "Answer: Because the end result of the rosacea
22 condition is due to inflammation of the skin.

23 "Question: Okay. Can you tell us what
24 expectations of success, if any, you had when you treated
25 the rosacea of the patient of Exhibit A with this twice

Talton - designations

1 daily dose of Periostat?

2 "Answer: I expected her skin to get better.

3 "Question: And why did you have that

4 expectation?

5 "Answer: Based on my own personal usage as well
6 as my knowledge of the fact that rosacea is an inflammatory
7 skin condition, I anticipated that the Periostat would make
8 her skin better.

9 "Question: In the dermatology field, based upon
10 your experience, have tetracycline compounds been used
11 off-label to treat skin conditions?

12 "Answer: Yes.

13 "Question: Has that been a rare practice, a
14 common practice, or somewhere in between?

15 "Answer: Very common practice.

16 "Question: Was the method that you used to
17 treat the patient in Exhibit A an off-label use of
18 Periostat?

19 "Answer: Yes.

20 "Question: With respect to the patient of
21 Exhibit A, did you have any hesitancy in February of 2000 in
22 using Periostat to treat that patient for an off-label
23 purpose?

24 "Answer: No.

25 "Question: Why not?

Talton - designations

1 "Answer: Again, because I had often used
2 off-label -- often used prescriptions for off-label uses. I
3 had used Periostat myself and noticed my rosacea got better
4 and I had known that it was in the medical literature and
5 people had spoke about using it so I knew it was within the
6 realm of standard use.

7 "Question: According to your understanding, are
8 physicians subject to any ethical obligations that they oh
9 their patients?

10 "Answer: Yes.

11 "Question: According to your understanding in
12 February of 2000, can you tell us whether or not you had an
13 ethical obligation to only use patient treat methods that
14 you believed would work for their intended purpose?

15 "Answer: Yes.

16 "Question: And according to your understanding
17 in February of 2000, can you tell us whether or not you had
18 an ethical obligation to refrain from using patient
19 treatment methods that you did not expect would work for
20 their intended purpose?

21 "Answer: Yes.

22 "Question: Can you tell us whether or not it's
23 been your experience that if the treatment that you
24 prescribed for patients does not work, you hear back from
25 the patient?

Talton - designations

1 "Answer: Yes, that's almost always the case.

2 "Question: If the treatment works, what is
3 the -- what is your experience about whether you hear back
4 from the patient concerning the condition that you treated?

5 "Answer: You usually never hear back when it
6 works.

7 "Question: After using the method of Exhibit A
8 to treat the patient of Exhibit A, did you ever see that
9 patient again for their rosacea condition?

10 "Answer: No.

11 "Question: Did you ever see the patient of
12 Exhibit A for any other reason following your treatment of
13 their rosacea condition?

14 "Answer: Yes.

15 "Question: And when, relative to the
16 February 2000 time frame of the patient record of Exhibit A,
17 did you next see that patient?

18 "Answer: In 2004.

19 "Question: And for what condition did you see
20 her then?

21 "Answer: She wanted me to do a -- it's called a
22 mole check. She wanted me to check her moles to make sure
23 none of them were cancerous.

24 "Question: Did she say anything at all about
25 her rosacea condition at that time?

Talton - designations

1 "Answer: She did not.

2 "Question: Did you notice anything about her
3 rosacea condition at that time?

4 "Answer: I did not.

5 "Question: Yes. Can you tell us whether or not
6 you drew any conclusions about whether or not the patient of
7 Exhibit A had taken the Periostat as you prescribed it to be
8 taken in February of 2000?

9 "Answer: I concluded that she had taken it.

10 "Question: And what was the basis for that
11 conclusion?

12 "Answer: The fact that I didn't get a call
13 back. Usually if someone can't take the medicine or doesn't
14 take the medicine they will call me back and ask for another
15 medicine.

16 "Question: You mentioned earlier, Dr. Feldman,
17 that you had taken Periostat in the December '99,
18 January 2000 time frame. When did that prescription expire?

19 "Answer: I took it for -- the periodontist gave
20 me a prescription for one month, for 30 days, but he told me
21 to keep taking it, and so what I did is I contacted the
22 CollaGenex Corporation and asked them if they would send me
23 professional courtesy samples of Periostat so I could keep
24 taking it and --

25 "Question: When -- I'm sorry. Go ahead.

Talton - designations

1 "Answer: -- and they did. They sent me.

2 "Question: When did you CollaGenex for these
3 professional courtesy samples?

4 "Answer: In January.

5 "Question: Of?

6 "Answer: 2000.

7 "Question: Did you get a reply from CollaGenex?

8 "Answer: Yes. They were kind enough to send me
9 three or four bottles of 100 tablets of Periostat.

10 "Question: So you had 3 to 400 tablets?

11 "Answer: Yes.

12 "Question: Did you take those?

13 "Answer: Yes.

14 "Question: Throughout the year or during the
15 year 2000?

16 "Answer: Yes.

17 "Question: And while you were taking them, can
18 you tell us whether or not you noticed anything about your
19 rosacea condition?

20 "Answer: My rosacea condition improved.

21 "Question: And 3 to 400 tablets lasts 150 to
22 200 days, approximately?

23 "Answer: Yes.

24 "Question: So that would take you through
25 roughly June and July of that year?

Talton - designations

1 "Answer: Yes.

2 "Question: Did you cease taking Periostat once
3 these professional courtesy samples were exhausted?

4 "Answer: Yes.

5 "Question: Did you ever take Periostat again
6 for your rosacea condition?

7 "Answer: I did. About maybe a year and a half
8 to two years later I had a flare-up, and for a month or two
9 I took another course of twice-a-day Periostat.

10 "Question: And where did you get the Periostat
11 at that time?

12 "Answer: Same. From the -- I asked for more
13 professional samples.

14 "Question: From CollaGenex?

15 "Answer: Yes.

16 "Question: Now, you mentioned there was
17 inflammation rosacea. Do you consider rosacea an
18 inflammatory disease?

19 "Answer: Yes.

20 "Question: Is it a chronic disease?

21 "Answer: Yes.

22 "Question: So would you consider it a cyclical
23 disease where there are periods of flare-ups and periods of
24 remission?

25 "Answer: Yes.

Talton - designations

1 "Question: And if I left untreated, will there
2 still be periods of flair-ups and periods of remission?

3 "Answer: Yes.

4 "Question: Do you currently prescribe Periostat
5 for the treatment of rosacea?

6 "Answer: I do not.

7 "Question: Why not?

8 "Answer: Because subsequently Oracea was
9 developed and that replaced Periostat in the use for
10 rosacea.

11 "Question: So you do prescribe Oracea?

12 "Answer: Yes.

13 "Question: About what percent of your rosacea
14 patients do you prescribe Oracea to? It's a very
15 inarticulate sentence.

16 "Answer: I would say 35 percent.

17 "Question: And about how many prescriptions is
18 that on, say, a monthly basis?

19 "Answer: I would say 15 to 20.

20 "Question: And you said you stopped or you
21 don't prescribe Periostat because Oracea is available. Do
22 you consider Oracea a better treatment option than
23 Periostat?

24 "Answer: Yes.

25 "Question: Why is that?

Talton - designations

1 "Answer: Because it is time released and you
2 only have to take it once daily.

3 "Question: And what is the once daily? Why do
4 you consider that better?

5 "Answer: There are many studies that show that
6 if you take a medicine once daily as opposed to twice daily
7 that you have a better compliance rates by the patients.

8 "Question: And therefore better improvement in
9 the rosacea condition?

10 "Answer: Yes.

11 "Question: How do you determine whether a
12 particular medication is working for a specific patient?

13 "Answer: We examine the skin and/or they tell
14 us that there is less redness. I mean it's not a
15 difficult -- it's not a difficult or a cult kind of
16 diagnosis. It's pretty clear they get less red. Their skin
17 is less red and their nose doesn't have pimples. They, you
18 know, don't get flushed as easily.

19 "Question: When was the last time that you
20 prescribed Periostat? Do you recall?

21 "Answer: I would say in the early 2000s, maybe
22 2001, 2002.

23 "Question: Does that include generic
24 20 milligrams of doxycycline?

25 "Answer: Yes.

Talton - designations

1 "Question: Are you aware of when Oracea came on
2 the market?

3 "Answer: Not to the exact date, no.

4 "Question: Why did you stop prescribing
5 Periostat in 2002?

6 "Answer: Because I think that's when Oracea --
7 around that time is when Oracea became available.

8 "Question: How commonly did you prescribe
9 Periostat for your rosacea patients prior to the
10 availability of Oracea? And by Periostat, I mean or the
11 generic doxycycline.

12 "Answer: I would say maybe three to five
13 patients.

14 "Question: Why is it that you prescribed
15 Periostat to three to five patients but now prescribe Oracea
16 15 to 20 times a month?

17 "Answer: Well, because at the time it wasn't as
18 well -- it was the infancy of it. People had just started
19 thinking about the antiinflammatory effects of doxycycline,
20 and, as you know, data became available, and then time went
21 on and it was becoming more and more a typical treatment of
22 rosacea.

23 "Question: So it was not a typical treatment as
24 of 2000?

25 "Answer: No.

Talton - designations

1 "Question: So one of the impetus in trying a
2 medication for the first time is to see how it works in the
3 patient?

4 "Answer: Yes.

5 "Question: And that was the case with the
6 February 19th chart that we saw you prescribe Periostat to
7 that patient to see how it would work?

8 "Answer: Yes.

9 "Question: Now, why would you prescribe an
10 off-label treatment instead of using a standard therapy or
11 an improved treatment?

12 "Answer: Sometimes you think it might work
13 better. For example, in this case if it's a lower dose of
14 doxycycline you might hypothesize that there will be less
15 side effects. For example, with doxycycline, there are
16 commonly GI side effects such as heartburn and nausea and
17 stomach upset and photo sensitivity where at a lower dose
18 you wouldn't expect to see it as much.

19 "Question: Now, I think you testified bench
20 that as of -- I can't recall if it was 99 or 2000 -- that it
21 was not believed that rosacea had a -- that bacteria were
22 involved in rosacea; is that correct?

23 "Answer: Correct.

24 "Question: During that time frame, wasn't it
25 thought that H. pylori could be an organism involved in the

1 disease?

2 "Answer: It was a hypothesis but it had never
3 been proven."

4 THE COURT: Mr. Reed, let's go ahead and cut it
5 for tonight.

6 We have reached the end of our day together.

7 I'll leave it to you to mark where we stopped, and we'll
8 begin tomorrow with picking up the deposition at the time
9 where we are, and we will meet again at 8:30 tomorrow
10 morning. Have a good night.

11 (Trial proceedings conclude at 6:00 p.m.)

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14 I hereby certify the foregoing is a true and accurate
15 transcript from my stenographic notes in the proceeding.

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/s Brian P. Gaffigan
Official Court Reporter
U.S. District Court

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